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MYOCARDITIS IN THE NEWBORN INFANT

A STUDY OF AN OUTBREAK ASSOCIATED WITH COXSACKIE GROUP B VIRUS INFECTION IN A MATERNITY HOME IN JOHANNESBURG

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IN OCTOBER and November, 1952, a number of newborn infants became ill while in, or soon after discharge from, the maternity home in which they were born. Of ten babies affected, six died after an acute fulminating illness ending in circulatory collapse. The maternity home concerned was modern, well equipped, and well run, and no cause for criticism of the staff was apparent. At the stage in which we came into the picture five of the patients had already run their course without the maternity home authorities having any knowledge that a communicable disease was raging in the nursery. Three of them had sickened at home after their discharge, subsequently dying; one had suffered and recovered from an illness manifesting toxemia and diarrhea one month previously in the maternity home; the remaining one had sickened and died suddenly one week before while still in the maternity home. Three of the four babies who died had been submitted to autopsy, but, as no suspicion at that stage had been aroused regarding an epidemic factor, no viral studies were carried out. Furthermore, the information in regard to these five infants was collected in retrospect. Having been alerted, however, we studied the next five cases in detail. Of these, two patients died and three recovered. Myocarditis, clinical and/or histological, was evident in four and encephalitis in one. In four of the cases evidence of a Coxsackie group B virus infection was found.

A summary of the clinical findings appears in Table I. Cases 6 to 10 were not seen by us and the history was obtained from the institutional records and the doctors concerned.

CASE HISTORIES

CASE 1.—This infant was born on Oct. 29, 1952, weighing 8 pounds 7 ounces, labor being normal. Breast

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TABLE I

NO.	AGE AT ONSET OF ILLNESS (DAYS)	SYMPTOMS AND SIGNS	ECG	OUTCOME	NECROPSY	SPECIAL STUDIES	REMARKS
1	9	Temperature 103° F.; tachycardia—220 per minute; cyanosis; dyspnea; râles in lungs	—	Died in four hr.	Pneumonia; hemorrhage in brain and suprarenal glands; heart microscopically showed myocarditis	Coxsackie B lesions in baby mice inoculated with brain suspension	Clinical and histological evidence of myocarditis
2	17	Malaise; toxemia; tachypnea; cyanosis; tachycardia—220 per minute; hepatomegaly edema of legs	Rate 220; ventricular tachycardia —rate 150	Died in 24 hr.	Heart enlarged due to dilatation of all chambers. Microscopically showed evidence of myocarditis. Focus of encephalitis	Coxsackie B lesions in baby mice inoculated with brain suspension	Clinical, electrocardiographic, and histological evidence of myocarditis
3	8	Temperature 103° F.; pulse rate on admission 140. Two hours later became very ill; cyanotic; tachypneic; pulse 210. Temperature subsided on 8th da.	Rate 210 T_1 flattened	Recovered	—	Coxsackie group B virus recovered from feces	Clinical and electrocardiographic evidence of myocarditis. Positive culture for Coxsackie group B virus
4	11	Temperature 103° F.: tachycardia. Well in 48 hr.	Rate 210 T waves normal	Recovered	—	Coxsackie B lesions in baby mice inoculated with feces suspension	Was a contact admitted for observation. Put on cortisone, Terramycin, penicillin and streptomycin. Sickened sharply after 3 da. but recovered quickly
5	9	Fed indifferently on 2 da.; sudden collapse; fever; cyanosis	—	Died within 5 hr. of onset of acute phase	Heart enlarged due to dilatation of all chambers. Microscopically showed evidence of patchy myocarditis	—	This was the first proved case of myocarditis

6	7	Sudden temperature 104° F. and off feedings for 2 da. Temperature settled by 3rd da. Improved and discharged from maternity home apparently well. 2 da. later very ill. Ordered to hospital but arrived dead	—	Died after 5 da., but within a few hours of onset of acute phase	—	—	District surgeon permitted burial—death by natural causes. Not seen by us. History from institutional records. This was the first case of the outbreak. The gravity of the second phase of the illness is well illustrated
7	5	Pyrexia; tachycardia; mucus in the stools at age 5 da. Treated with penicillin and sulfonamide. Four days later again febrile for a day. Discharged fit a day later	—	Recovered	--	—	Not seen by us. History obtained from institutional records Typical recrudescent character
8	7	Discharged from maternity home fit after an illness of loose stools and temperature on 7th da. Sickened suddenly 8 da. later. Died by time doctor arrived	—	Died 8 da. after original onset but within a few hours of onset of acute phase	Macroscopically—suggested acute fulminating broncho-pneumonia but no microscopic studies done	—	Not seen by us. History obtained from institutional records. Typical recrudescent character
9	16	Discharged from maternity home apparently fit on 9th da. 7 da. later took ill suddenly. Collapse. Rushed to hospital and died a few minutes after admission	—	Died in a few hours	Heart pale and flabby. Brain congested. Petechial hemorrhages in stomach and intestines. Mucopus in bronchi. No microscopic studies done	—	Not seen by us. History obtained from institutional records.
10	9	Fever; meningism and bulging fontanel. C.S.F. showed pleocytosis. Tachycardia	—	Recovered	—	—	Not seen by us. History obtained from institutional records. Encephalitis. Was breast fed by mother of Case 1. Tachycardia suggests myocarditis in addition

feedings were well taken, with gain in weight until the age of 8 days. On November 7, at 5:15 P.M., the infant became ill suddenly, turned gray, and had a distressed cry. When seen at 6 P.M. the baby was in great distress, cyanosed and dyspneic, and had a temperature of 103° F. The heartbeat was forceful and tachycardia extreme, the rate being over 220 beats per minute. The sounds were normal and cardiac enlargement was not detected. The blood pressure was 80/0. Marked inspiratory subcostal recession and scattered râles in both lungs were present. The abdomen was slightly distended and palpable swellings were noted in the region of both kidneys. The anterior fontanel was normal. A clinical diagnosis of viremia, myocarditis, suprarenal hemorrhage, and pneumonia was suggested. The infant was placed in an oxygen tent and put on Terramycin and cortisone, but died at 9:50 P.M.

No laboratory tests were done as the baby was in extremis when first seen.

Detailed findings of the post-mortem examination are described in a following section of this paper. Microscopical evidence of myocarditis was present and special studies suggested the presence of a Coxsackie group B virus infection. Baby mice inoculated with a suspension of the brain showed lesions similar to those produced by this virus.

CASE 2.—This infant, weighing 8 pounds 1 ounce, was born on Oct. 22, 1952, by spontaneous normal delivery of a primiparous mother whose pregnancy had been healthy. The infant fed normally at the breast, appearing perfectly well in the maternity home, and was discharged on the tenth day. On November 8, one week later, she went off color, slept all day and refused her feedings. During the night she was fretful, the nose was blocked, and the breathing rapid and distressed. She refused her 6 A.M. feeding, appeared ill, and sweated a great deal. The next feeding was again refused, the cry being feeble. No vomiting occurred, and the stools appeared normal. By 11 A.M. the skin had become blue and mottled, the hands and feet were cold, and considerable sweating continued. At this stage, she was first seen by a doctor who transferred her to the Children's Hospital urgently.

On admission the infant was moribund. A pronounced tachycardia was present, the rate being 220 per minute, the rhythm suggestive of a gallop. The heart sounds were normal; cardiac enlargement could not be evaluated. The systolic blood pressure was 70 and the diastolic could not be determined. The lungs were resonant, no adventitious sounds being heard and no clinical signs of pneumonia, atelectasis, or other pulmonary disease could be detected. The liver was enlarged and both kidneys were palpable. The lower limbs were edematous. The skin was mottled and cyanotic. Injections of penicillin, streptomycin, and cortisone were given. Shortly after admission, the heart rate was observed to be slowing and an electrocardiogram showed ventricular tachycardia—rate 150 (Fig. 1). The electrocardiogram was still being taken when the heart slowed and the child died suddenly one hour after admission, before a portable x-ray could be arranged (Fig. 2). The clinical diagnosis was one of myocarditis and suprarenal failure associated with an acute infection.

Investigations.—Blood taken shortly after admission was sterile. The blood urea was 59 mg. per cent. Specimens of heart blood and lung puncture fluid taken some hours later at the autopsy were also sterile. A coliform bacillus, grown from the ascitic fluid, was regarded as a post-mortem contaminant.

The post-mortem findings are given in the following section of this paper. Myocarditis was present and, again, evidence suggestive of Coxsackie group B virus infection was found.

CASE 3.—This infant, an illegitimate child, was delivered by cesarean section on Nov. 1, 1952, weighing 5 pounds 9 ounces. She remained well until discharge from the maternity home on November 8, and was being taken by her doctor to the home of her adopting parents when it was noticed that the child was febrile. She was therefore admitted to the Children's Hospital.

On admission her temperature was 103° F., but she did not look ill. There was no anemia, cyanosis, or jaundice. The pulse rate was 140, regular, and the respiratory rate 38 per minute. The heart sounds were normal and there was no cardiac enlargement. No abnormality was detected in the lungs, abdomen, and nervous system.

In view of a known death at the maternity home the previous evening, an acute viremia was suspected, and treatment with penicillin, streptomycin, Terramycin, and cortisone was instituted.

The infant became worse after admission and two hours later was cyanotic and tachypneic. The heart rate was very rapid (210 per minute) and the action forceful. The electro-

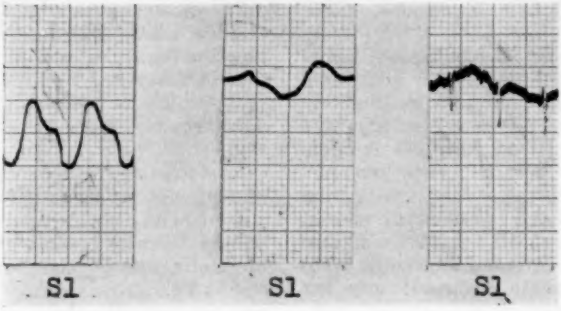

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Electrocardiogram showing ventricular tachycardia. Case 2.
Fig. 2.—Electrocardiogram showing slowing of heartbeat at death. Case 2.
Fig. 3.—Electrocardiogram showing flattened T wave. Case 3.

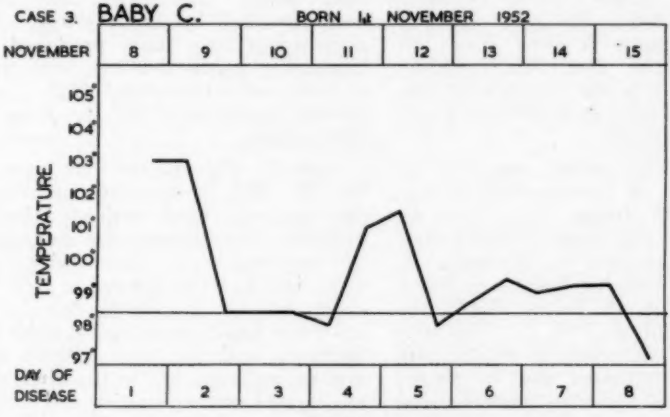

Chart I.

cardiogram showed flattened T waves in the first standard lead (Fig. 3). The liver did not enlarge and edema was not present. On the eighth day the temperature subsided, the pulse rate dropped, and the infant's general condition improved remarkably. Her electrocardiogram became normal and she was discharged, apparently fit, fourteen days after admission. (See Chart I.)

Investigations.—Blood count: hemoglobin was 15.5 grams per cent; leukocytes 10,700 per cubic millimeter; neutrophils 46 per cent; lymphocytes 50 per cent. Blood culture was negative. Blood serum: virus complement fixation tests for herpes simplex, mumps, and lymphocytic choriomeningitis were all negative. Urine: nil abnormal detected. Stool: a virus of the Coxsackie group B was isolated.

Comment.—As the infant sickened on the eighth day of life, the incubation period was eight days or less. Marked tachycardia and electrocardiographic changes were the evidence for myocarditis. Recovery of the Coxsackie group B virus from the feces suggested that this infection was the cause of the illness, as is discussed more fully in a following section of this paper.

CASE 4.—This infant was born on Oct. 30, 1952, by forceps delivery, the birth weight being 7 pounds 14 ounces. She had kept perfectly well and was discharged on November 8, when the maternity home was being emptied after an infant death the previous evening (Case 1). The parents were instructed to report any suspicious symptoms and to record the rectal temperature morning and evening.

On November 10 the parents reported that the baby appeared listless and had only taken 2 ounces at each feeding that day. The temperature was 99.6° F. Although the infant did not appear ill and the examination was negative, she was admitted to the Children's Hospital on the same day. Moreover, in order to get some lead on the preventive value of treatment currently being used therapeutically on another patient (Case 3) she was also put on penicillin, streptomycin, Terramycin, and cortisone.

The child remained well for three days, when she sickened very suddenly, with a temperature of 103° F. and a tachycardia. An electrocardiogram showed a rate of 210 per minute, but no significant T-wave change. The temperature and pulse rate settled in forty-eight hours, and the infant progressed normally. She was discharged thirteen days after admission.

Comment.—This patient, a contact under close observation, was admitted with slight temperature and anorexia which settled quickly. Prophylactic use of streptomycin, penicillin, Terramycin, and cortisone did not prevent the child sickening suddenly three days later, with high temperature and marked tachycardia. However, the infant did not become toxic and the illness settled in forty-eight hours. The illness may have been modified by the therapy. Lesions resembling those produced by Coxsackie group B virus were seen in baby mice inoculated with a suspension prepared from the feces of this patient.

CASE 5.—This infant was born on Oct. 22, 1952, by spontaneous normal delivery, the birth weight being 9 pounds. She thrived for five days, did not take her feedings well on the fifth day, but the following day fed normally. On the eighth day the infant was again reluctant to take her feedings and she was offered glucose-saline instead. On the ninth day the baby became feverish and took a bad turn at 8:30 P.M. The color became gray and the infant collapsed. Coramine and Crysticillin were given without effect and the child died five hours later.

This was the first infant to die in the maternity home. Her tissues were subjected to minute histological study and lesions of widespread but patchy myocarditis were found. As

a viral cause at that time was not suspected no further studies were made.

CASE 6.—This infant was born on Oct. 8, 1952, weighing 8 pounds, the labor being normal. The baby thrived for the first week, then took a sudden bad turn one evening, developing a temperature of 104° F. Intramuscular penicillin was prescribed. Three days later the temperature had become normal and the child was discharged the following morning, weighing 8 pounds 11 ounces. The same evening the family doctor was called because the baby was not taking feedings. The temperature was found to be 99° F. and the spleen was palpable. Intramuscular penicillin was given. The following day the child appeared better. One day later the doctor was sent for urgently, owing to sudden deterioration, and on arrival he found the baby in extremis. The infant died on the way to the Children's Hospital. (See Temperature Chart II.)

Comment.—This infant, the first case of the outbreak, exhibited the intermitent course and sudden fatal collapse seen in other infants in this series, suggestive of an illness of viral origin.

CASE 7.—Born on Oct. 14, 1952, by spontaneous normal delivery, this infant weighed 6 pounds 12 ounces and thrived for the first five days. At this stage the baby was found to have a temperature of 101° F. and some mucus in the stools. Penicillin and Sulfatriad were prescribed. The infant improved and the temperature settled, remaining normal for three days. On the fourth day the temperature again rose to 101° F. but settled the following day, and the child was discharged from the maternity home, continuing to thrive thereafter. The illness of this patient again demonstrated its typical recrudescent character.

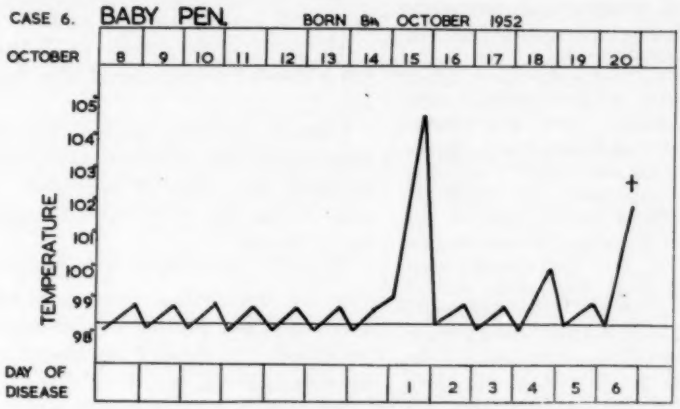

Chart II.

CASE 8.—This infant was born on Oct. 17, 1952, labor being normal, and the birth weight 6 pounds 15 ounces. The baby progressed well for the first six days and then developed a temperature of 99.8° F. and loose stools. No therapy was instituted and the child was discharged two days later, weighing 7 pounds 7 ounces. Eight days after discharge the infant took a sudden bad turn. The family doctor was called but when he arrived the child was moribund and died soon after. A post mortem showed bronchopneumonia macroscopically. No histological studies were done. The recrudescent character of the illness is again apparent.

CASE 9.—Born on Oct. 19, 1952, labor being normal, this infant weighed 6 pounds 11 ounces at birth, and progressed satisfactorily, being discharged on the ninth day, weighing 6 pounds 14 ounces. One week later the child was admitted to the Children's Hospital in collapse and died soon after admission. A post mortem was performed but no microscopical studies were carried out. The heart muscle was pale and flabby, the brain congested, and petechial hemorrhages were present in the stomach and intestine.

CASE 10.—This infant was born on Oct. 31, 1952, by spontaneous normal delivery. She was breast fed by the mother of the patient in Case 1 and thrived for the first eight days, when she developed a temperature and bulging fontanel. She was transferred to the Johannesburg Fever Hospital and on admission was found to have a temperature of 102.8° F. No abnormalities were noted in the ears, nose, or throat. The heart rate was increased, but the sounds were normal. The lungs were clear and no abnormalities of the abdomen were detected. The fontanel was bulging, but no neck stiffness was found. The cerebrospinal fluid was clear. Cell count showed 305 lymphocytes per cubic millimeter. The protein was 82 mg. per cent, the chloride 125 meq. Sugar was 40 mg. per cent.

No pathogenic bacteria were detected on culture of this fluid. Unfortunately, virus isolation was not attempted. Nose and throat swabs examined for *Corynebacterium diphtheriae* and *Streptococcus hemolyticus* gave negative results.

Intramuscular penicillin was prescribed and the temperature became normal on the fourth day of admission. Apart from a spike of temperature to 99.6° F. on the eighth day only, progress was uninterrupted and the infant was discharged from hospital twelve days after admission.

Comment.—This case is of particular interest because in addition to the tachycardia there were indications of a meningoencephalitis as shown by the bulging fontanel, the pleocytosis, and the increased protein content of the cerebrospinal fluid.

PATHOLOGY

Autopsies were carried out on three cases, viz., Cases 1, 2, and 5, 48, 15, and 32 hours after death, respectively.

All three infants appeared well nourished and showed no external evidence of disease, injury, or congenital abnormalities. The umbilicus appeared healthy in each case.

The peritoneum and sac in all three cases showed no significant abnormality.

Cases 2 and 5 showed a few subpleural petechial hemorrhages on both parietal and visceral surfaces. In Case 1, the pleural surfaces showed a loss of luster.

Cases 2 and 5 showed a slight excess of pericardial fluid and Case 2, in addition, showed subpericardial petechiae. In Case 1, no significant abnormality was noted.

All three hearts were enlarged, owing to dilatation of both the auricles and ventricles. In Case 2 and Case 5 the myocardium was thickened and congested, but in Case 1 it appeared pale. Apart from slight thickening of the left ventricular endocardium in Case 2, no other abnormalities were noted.

The ductus arteriosus was patent in each case. The aorta and venae cavae appeared healthy.

The upper respiratory tract, including the nasal and accessory sinuses, and the bronchial tree, showed no significant pathological abnormality.

In all cases the lungs were congested. In Cases 1 and 2 areas of

partial atelectasis were noted, whereas in Case 5 the lungs appeared to be fully aerated.

No abnormalities were noted in the stomach and intestines.

In all three cases the liver showed congestion only.

The gall bladder, bile ducts, and pancreas revealed no gross abnormality.

Apart from slight congestion of the kidneys no significant pathological changes were noted.

The spleen was congested in each case.

No enlarged lymph glands were found.

Case 5 showed evidence of a small subaponeurotic hemorrhage over the right parietal and occipital bones, but in this and the other two cases the skull showed no abnormality.

The meninges and sinuses were normal.

The brains apart from slight edema and congestion appeared healthy.

The thyroid and pituitary glands revealed no abnormality.

In Cases 2 and 5 the suprarenal glands were congested. In Case 1 gross hemorrhage was noted.

HISTOPATHOLOGY

The following organs and tissues were examined in all three cases: (1) heart, (2) lungs and pleurae, (3) liver and peritoneum, (4) suprarenal glands, (5) kidneys, (6) brain.

In addition the following organs were examined in two cases: (1) pancreas, (2) spleen, (3) thymus, (4) thyroid, (5) small intestine.

In one case only the following additional organs were also examined: (1) parathyroid, (2) testis and epididymis, (3) trachea, (4) stomach, (5) aorta.

The heart in all three cases showed essentially similar features, but varying in extent and intensity. In Case 1 the pericardium showed an occasional chronic inflammatory cell, but in the other two cases it showed no significant pathological change. The endocardium in Case 5 appeared normal; in Case 2 it was thickened and edematous and showed a focal infiltration by lymphocytes, a few polymorphonuclear leukocytes and eosinophil leukocytes; the endocardium in Case 1 showed no thickening or edema, but there were a few foci of infiltration by lymphocytes, large mononuclear cells, and eosinophil leukocytes.

The myocardium showed congestion in Case 2 only. Patchy interstitial edema was observed in all three cases. The most striking feature, however, was a pleomorphic cellular infiltrate. In Cases 2 and 5 it was patchy, but in Case 1 the infiltrate was diffuse, although it showed a tendency to be more concentrated in certain areas (Fig. 4). The inner third of the myocardium appeared to be more heavily involved than the outer two-thirds. The infiltrate consisted of a large number of large mononuclear cells with vesicular nuclei, some of which showed vacuolation of their cytoplasm, a moderate number of histiocytes with basophilic cytoplasm, a few lymphocytes, and occasional neutrophil polymorphonuclear leukocytes, eosinophils, and plasma cells. Fibroblasts were not observed (Fig. 5). In sections stained with Giemsa, spherical, baso-

philic granules resembling inclusion bodies were seen in the cytoplasm of some of the histiocytes (Fig. 6).

For the study of the muscle fibers, sections were stained with van Gieson, phosphotungstic acid hematoxylin (P.A.H.), and Heidenhain's hematoxylin. With the van Gieson stain no abnormality was noted. However, with the hematoxylin stains, examination under low magnification revealed areas in which the muscle fibers had lost their affinity for the stain. These changes were more widespread with the Heidenhain's than with the P.A.H. stain. In some areas there appeared to be only a diminution in staining properties, whereas in others it was completely lost. The change from well-stained fibers to nonstaining fibers was sudden or gradual. In the latter case it would seem that the first change was a diminution of the affinity of the myofibrils for the stain, the longitudinal striations becoming less obvious and eventually disappearing. At the same time the transverse striations became more prominent and wider. Eventually the transverse striations also disappeared and the muscle fiber appeared homogeneous. It then disintegrated and ultimately empty sarcolemmal sheaths were left. The nuclei showed progressive pyknosis followed by complete dissolution. An interesting feature was that in some of the infiltrated areas the staining properties were normal, but in all areas which failed to stain, an infiltrate was present. It would appear, therefore, that the infiltrate preceded the changes in the muscle fibers.

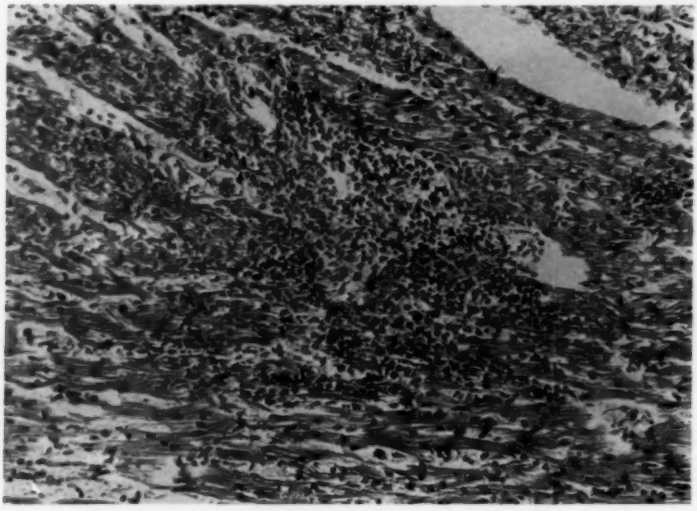

Fig. 4.—Section of heart showing focal myocarditis.

No evidence of calcification, muscle regeneration, or of nuclear proliferation was observed in any of the cases.

In Case 2 these changes were found in both ventricles, the interventricular septum and auricles. In the other two cases only the left ventricles were examined.

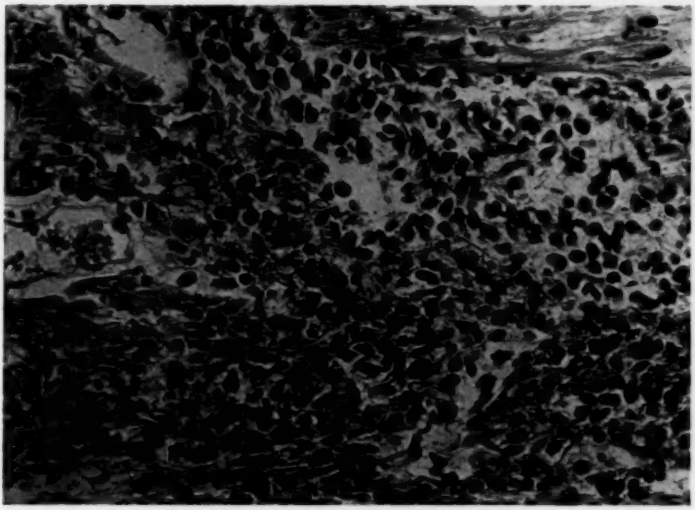

Fig. 5.—Section of heart showing character of cellular infiltrate.

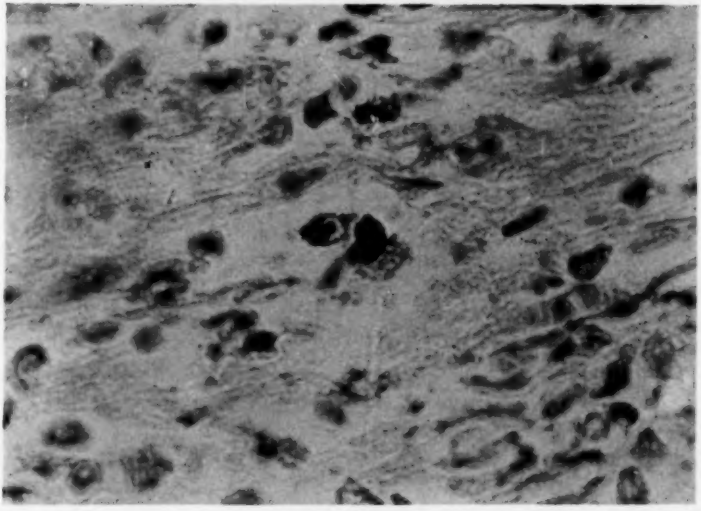

Fig. 6.—Section of heart showing basophil granule in cytoplasm of histiocyte.

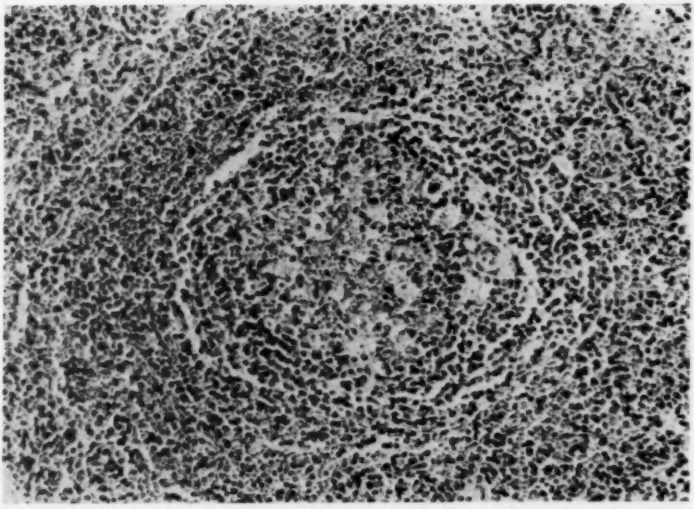

Fig. 7.—Section of spleen showing central necrosis of Malpighian corpuscle.

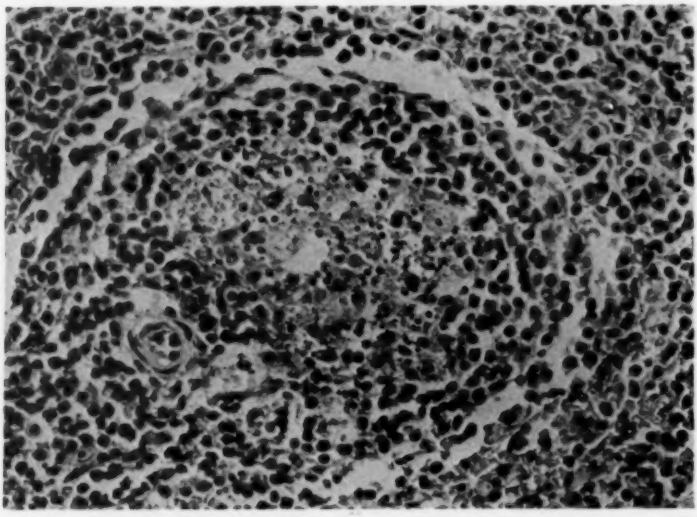

Fig. 8.—Section of spleen showing character of central necrosis of Malpighian corpuscle.

In the one case in which the aorta was examined, it was normal in appearance.

The splenic capsule and trabeculae in Case 2 appeared normal. The pulp was congested and the sinuses were dilated, but no reactive change was observed in the littoral cells. The Malpighian corpuscles were increased in size and in number. A few, apart from this increase in size, were normal in appearance. The majority, however, showed a definite central necrosis (Fig. 7). All stages of development of this necrosis could be seen. The earliest change was pyknosis of the nuclei of some of the lymphocytes. This progressed to karyorrhexis and complete disintegration of the cells. Pari passu with the pyknosis there was a proliferation of reticulum cells. In the final stages the corpuscle consisted of a central necrotic area containing nuclear debris surrounded by a zone of reticulum cells. Peripheral to this there were some remaining lymphocytes. There was no associated acute inflammatory reaction and no periarteritis (Fig. 8).

In Case 5 some of the Malpighian corpuscles showed a slight increase in reticulum cells, a few pyknotic nuclei, and some nuclear debris. The pulp was congested.

The spleen was not examined in Case 1.

In Case 2 only were lymph glands sectioned. These showed severe congestion, hemorrhages in the follicles and in the medulla. A few follicles showed central necrosis with abundant nuclear debris. No increase in reticulum cells was noted (Fig. 9).

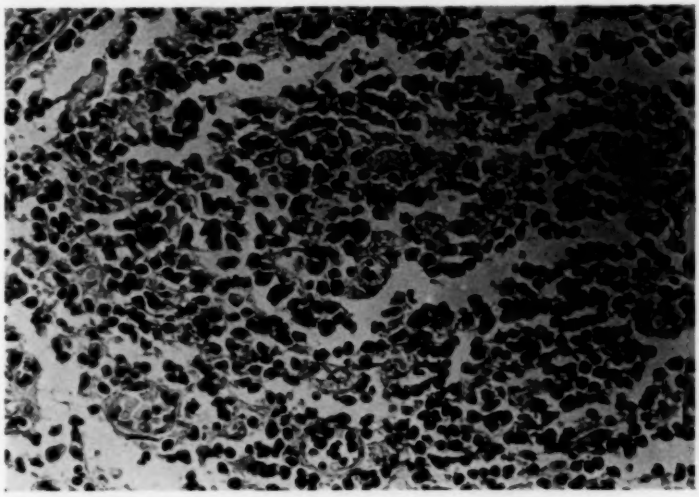

Fig. 9.—Section of lymph gland showing involvement of follicle.

The suprarenal glands of all three cases showed intense congestion. In addition, in Case 5 there was a small hemorrhage and in Case 1 there was a massive hemorrhage.

The leptomeninges in all three cases showed no significant change.

Brain: In two cases there was slight edema. In Case 2 there were well-marked congestion and numerous petechial hemorrhages in the white matter. In addition, the same case showed an infiltrate consisting of lymphocytes and polymorphonuclear leukocytes around one of the capillaries (Fig. 10).

Sections taken from the lungs of all three cases showed severe congestion of the alveolar capillaries and extravasation of edema fluid into the alveoli. The alveoli also contained alveolar phagocytes. The bronchial and bronchiolar epithelium was desquamated. The interstitial tissue showed no significant pathological change. Case 5, in addition to the above findings, showed the presence of foci of partial atelectasis and extravasation of red blood cells into the alveolar spaces. These foci were surrounded by areas of compensatory emphysema.

The pleura in Case 2 and Case 5 showed no significant pathological changes, but in Case 1 it was thickened, edematous, congested, and angiectatic. It was infiltrated by a few polymorphonuclear leukocytes, monocytes, lymphocytes, and occasional eosinophil leukocytes. The surface was covered by a thin layer of fibrin in the depths of which were some polymorphonuclear leukocytes (Fig. 11).

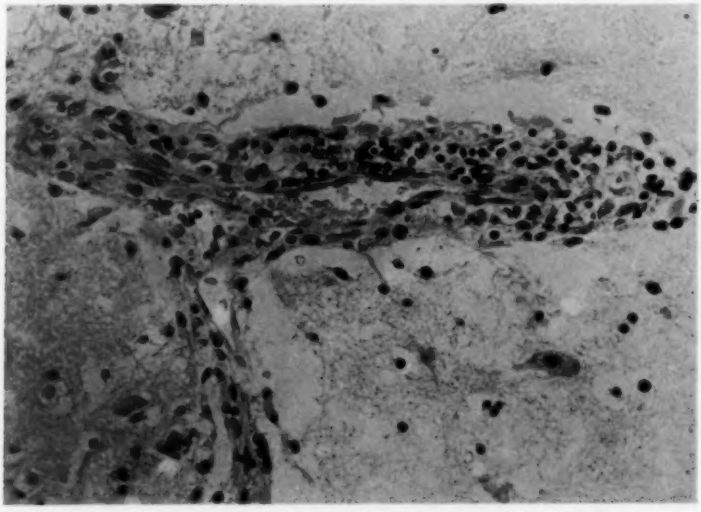

Fig. 10.—Section of brain showing inflammatory infiltrate.

The trachea, in the case examined, showed congestion of the mucosa only.

The livers showed no significant change in their capsules, bile ducts, or Kupfer cells. The portal tracts showed varying degrees of infiltration by polymorphonuclear leukocytes, eosinophil leukocytes, and lymphocytes. The sinusoids were congested and dilated. Two of the cases showed fatty change (Case 2

moderate and Case 5 slight). The peritoneal covering appeared normal.

Apart from patchy congestion of the glomeruli and interstitial tissue and some catarrh of the convoluted tubules, no significant changes in the kidneys were noted.

The thymus, thyroid, and parathyroid glands showed congestion only.

The testis and epididymis in Case 5 were congested. In the spermatic cord there was an infiltrate, mainly perivascular, but also to some extent in the interstitial tissue, consisting of lymphocytes, a few polymorphonuclear leukocytes, and eosinophil leukocytes.

The pancreas in the two cases examined were normal.

The stomach and small gut in the cases examined were autolyzed. As a Coxsackie virus infection was not suspected when these autopsies were performed, blocks of voluntary muscle and fat were not selected for section. However, sections from other organs, e.g., thyroid, kidney, etc., contained small fragments of voluntary muscle and fat and in these fragments no pathological changes were noted.

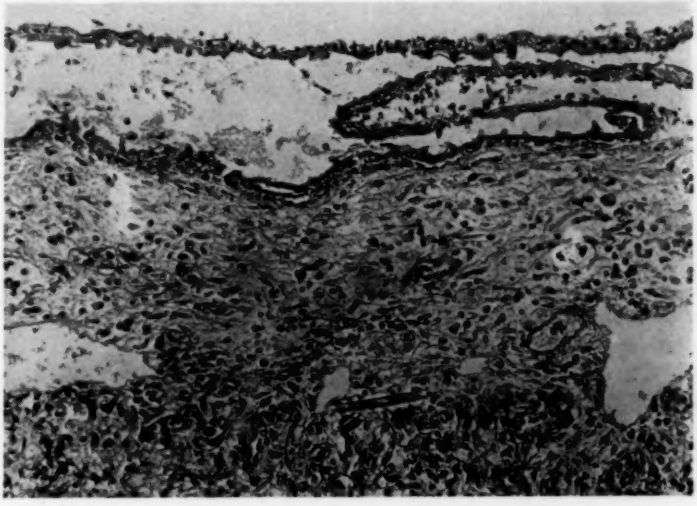

Fig. 11.—Section of pleura showing inflammatory infiltrate.

ETIOLOGICAL STUDIES

On being notified of this outbreak by Dr. Mundel of the Johannesburg City Health Department, arrangements were made to carry out a full laboratory investigation of the cases admitted to the Johannesburg Fever Hospital and the Transvaal Memorial Hospital for Children.

Full bacteriological studies were undertaken. These will not be reviewed in detail, but it may be noted that throat swabs were examined for hemolytic streptococci, diphtheria bacilli, and other pathogenic bacteria, with negative results. Blood cultures incubated for 14 days also gave negative results, and cultures of the feces

failed to reveal pathogenic bacteria. Cultures taken post mortem from the heart blood and spleen of Case 2 showed a growth of *B. coli* and *Staphylococcus albus*, but these were considered to be post-mortem invaders. The bacteriological investigation was therefore essentially negative.

VIRUS STUDIES

Virus studies were initiated at the same time as the bacteriological studies. It was known that the virus of encephalomyocarditis was the cause of myocarditis in mice and certain anthropoid apes, and that the Coxsackie group B viruses may cause focal myositis and focal myocarditis as well as necrosis and inflammation of the fat pad in baby mice. These viruses therefore were especially considered in our attempts to isolate a virus from the material submitted, but the methods used would, of course, detect a number of other viruses as well.

Material.—The following material was available for investigation:

1. Specimens of feces collected from Cases 3 and 4 while they were in hospital.
2. Blood cultures and blood taken from Cases 3 and 2.
3. Blood and portions of organs taken *post mortem* from Cases 1 and 2.

Unfortunately no specimens were taken from Case 5, whose histological sections gave the first indication that the cause of death was an acute focal but widespread myocarditis.

Method.—Specimen of feces:

The specimens of feces were treated as follows: A 10 per cent suspension was prepared in physiological saline. To this about one-fourth volume of anesthetic ether was added and allowed to act for twenty-four hours in a 4° C. refrigerator. The suspension was then spun for 1 hour at 3,000 revolutions per minute. The intermediate aqueous phase, now water clear, was transferred to a wide-mouthed specimen bottle which was placed in an incubator at 37° C. to evaporate most of the dissolved ether.

This suspension was then inoculated subcutaneously into a litter of one-day-old mice and intraperitoneally into eight adult mice.

The baby mice were checked daily for two weeks for weakness, tremors, or paralysis. If a baby mouse showed any of these signs, it was sacrificed and portions of the organs were fixed in Bouin's solution prior to preparing blocks for histological sections. A portion of the carcass was emulsified into a further litter of baby mice. Several passages were made in each case.

Post-mortem material:

Suspensions of the heart, brain, and blood removed post mortem from Cases 1 and 2 were prepared in physiological saline. One group of these suspensions was then treated with ether as described for the specimens of feces; another group was not treated with ether.

These suspensions were then inoculated into:

1. Fertile hen eggs
   a. On chorioallantoic membrane
   b. Into the yolk sac

   Several passages were made in each case.
2. Mice
   a. Adults, intraperitoneally and intracerebrally
   b. Baby mice, subcutaneously
3. Guinea pigs, intraperitoneally
4. Rabbits, intramuscularly

Except for the baby mice which were observed for fourteen days, these animals were observed for one month for signs of illness.

Results.—No virus was established in fertile egg passage. The rabbits and guinea pigs remained healthy. Indeed, the only significant findings were observed in the mice. These were:

Case 1. Adult mice inoculated intracerebrally with brain suspensions of Case 1. One of this group of mice was killed on the tenth day when it appeared to be ill. Sections of its brain showed focal lesions, which may have been related to the injection of foreign matter. Section of the pancreas showed early destruction of some acinar cells, associated with an acute inflammatory infiltration.

No passage was made from this mouse. Later it became apparent that the lesions of the pancreas resembled somewhat those produced by some strains of Coxsackie group B virus.

Case 4. Feces: One of the baby mice inoculated with the suspension prepared from Case 4 feces was observed to be weak on the eighth day after inoculation. It was sacrificed and sections of its organs were prepared. The section of the fat pad showed a small area of necrosis and early calcification and early acute inflammation. This lesion was similar to those produced by Coxsackie group B virus.

Case 3. Of the litter of baby mice inoculated with the original stool suspension from Case 3, one mouse was dead and eaten on the eighth day, two were weak, and one had tremors. The latter mouse was sacrificed. Sections showed fat necrosis and inflammation resembling that produced by Coxsackie group B virus.

Of the first passage litter inoculated with the carcass suspension from this mouse, one had tremors on the fourth day, and three were weak on the fifth day. One of these was sacrificed and a suspension from its carcass inoculated into a further litter. These mice also showed weakness and tremors. Sections from one showed necrosis and inflammation of the fat pad.

The virus so isolated was established in serial passage and has now been passaged a number of times. Some mice in each litter have shown weakness or paralysis and sections of the fat pad have shown typical lesions, including necrosis and acute inflammation. In mice which survive or are sacrificed after the eighth day, calcification of the fat pad is common. In addition, focal lesions of the brain are often seen. Frequently focal myocarditis with foci of acute eosinophil degeneration of the heart muscle with pyknosis of the nuclei, and associated with a slight acute inflammatory cell infiltration, has been observed. These lesions are also similar to those produced by Coxsackie group B virus.

Post-mortem material:

No virus was established in serial passage from the baby mice inoculated with the suspensions of the organs of Case 1 or 2. However, several passages were made, and later when sections of the viscera removed from the baby mice which had appeared weak or tremulous were examined microscopically, significant lesions were observed.

Case 1. Brain: A baby mouse of the first passage litter, inoculated

with carcass suspension prepared from the mouse of the litter inoculated with the original brain suspension, appeared to have tremors. It was killed on the fourteenth day after inoculation and sections of the organs were prepared. On examination, the sections of the brain showed focal lesions, including neuron degeneration, some neuronophagia and some perivascular inflammatory cell infiltration in the sera. These lesions were small and no conclusion as to their nature was made except that similar lesions had previously been observed in baby mice infected with known strains of Coxsackie group B virus. Sections of the fat pad showed degeneration and calcification, associated with an inflammatory cell infiltration. These lesions were localized to some lobes of the fat pad, the rest of which appeared relatively normal. However, these lesions resembled those caused by Coxsackie group B virus. Sections of the other organs showed no marked pathological changes.

Case 2. Brain: A baby mouse of the first passage litter was sacrificed on the tenth day after inoculation, when it appeared to be weak. Sections of its brain showed small focal lesions similar to those just described in a first passage mouse from Case 1. The other organs were not grossly abnormal.

These sections only became available several weeks after removal of the organs for histological examination, otherwise a greater effort would have been made to establish the agent responsible in serial passage in baby mice. This was not achieved. However, the lesions described above are similar to those caused by Coxsackie group B virus. Indeed, those of the fat pad are almost pathognomonic of this infection.

Identification of virus isolated from Case 3:

The virus isolated from the feces of Case 3 was identified in a baby mouse protection test.

Antisera prepared against strains of known Coxsackie type viruses, kindly sent to us by Dr. G. Dalldorf, were tested against virus suspensions prepared from baby mouse carcasses infected with Case 3 virus. In the tests 0.5 c.c. of neat serum was mixed with a mouse carcass suspension containing ±1,000 infective doses of virus. The mixture was shaken and incubated for 1 hour. Each mixture was then inoculated into five of a litter of seven or eight mice. The remaining two or three mice of the litter had their tails cut for identification and were inoculated with virus suspension only. These litters were observed for fourteen days. The results of the tests are given in Tables II and III.

TABLE II. BABY MOUSE PROTECTION TESTS WITH CASE 3 VIRUS AGAINST COXSACKIE GROUP B TYPE ANTISERA (DALLDORF TYPES)

ANTISERA	RESULT SURVIVORS/ TOTAL		INTERPRETATION
B1	0/5		No protection
B2	0/5		No protection
B3	5/5	5/5*	Full protection
B4	0/5		No protection
Normal serum control	0/8		No protection

*Result of repeat test.

It will be noted that the litters inoculated with the Case 3 virus + B1 antiserum, Case 3 virus + B2 antiserum, and Case 3 virus + B4 antiserum were not protected, while the litters inoculated with Case 3 virus + B3 antiserum survived, but all the control mice in each experiment died.

This experiment has been repeated and the result confirmed (Table III).

TABLE III. BABY MOUSE PROTECTION TESTS WITH CASE 3 VIRUS AGAINST COXSACKIE GROUP B TYPE ANTISERA (DALLDORF TYPES)

ANTISERA	RESULT SURVIVORS/ TOTAL	INTERPRETATION
B1	0/5	No protection
B2	0/5	No protection
B3	5/5	Full protection
B4	0/5	No protection
Normal serum control	0/16	No protection

CONCLUSION

It is thus concluded that the virus isolated from Case 3 is a Coxsackie group B type 3 virus.

The lesions observed in baby mice inoculated with the brain suspensions from the two fatal cases thus take on an added significance. It has already been noted that these lesions resembled those produced by Coxsackie group B virus. The fact that similar lesions were produced by fecal suspensions from two other infants who recovered, and from one of these a Coxsackie group B type 3 virus was isolated, suggests that these lesions were also produced by the same virus.

DISCUSSION

Epidemics among newborn babies in maternity institutions are now well recognized and documented.[1, 2] They usually take the form of diarrhea, less commonly of pneumonia or viremia. This is the first instance known to us of this form of outbreak in which the virus has been actually recognized and in which the myocardium has borne the brunt of the attack. Acute myocarditis of infective origin at all ages has been reported with increasing frequency and is now a well-recognized clinical entity.[3] Many viral diseases, e.g., mumps, poliomyelitis, influenza, measles, may have accompanying myocarditis. On the other hand, it is probable that many, at present, unidentified viruses are responsible for myocarditis either alone or as part of a generalized viremia.

The clinical evidence of acute myocarditis as seen in different diseases includes bradycardia, tachycardia, gallop rhythm, hypertension, a soft apical murmur or a first sound of poor quality. More particularly, a tachycardia out of proportion to the temperature is recognized as most significant evidence. Electrocardiographic changes consist for the main part of alteration in the T wave, either flattening or inversion, depressed S-T segment, low voltage QRS, disturbance of rhythm and conduction, such as partial and complete A-V dissociation, dropped beats, and nodal rhythm.

In infancy and childhood, myocarditis is often suspected when cardiomegaly is detected in association with normal heart sounds and electrocardiographic changes. The same diagnostic criteria hold good for endocardial fibroelastosis, glycogen storage disease of the heart, anomalous left coronary artery, and medial necrosis of the coronary arteries.[4] The last three conditions are rare. The clinical differentiation between myocarditis and fibroelastosis is more difficult and sometimes impossible. Both conditions are to be found in infancy and in both the brunt of the disease falls on the left ventricle.

In so far as the clinical picture of the cases in this outbreak is concerned, the general symptoms were those of a severe infection—sudden onset, high temperature, cyanosis,

dyspnea, tachycardia, profound toxemia, and a falling blood pressure. In some, death supervened within a few hours of the apparent onset. The clinical features suggestive of myocarditis were extreme tachycardia (rate 210 upwards per minute) and abnormal T_1 in the electrocardiogram. No cardiac murmurs were heard. Enlargement of the heart was not appreciable clinically, but was demonstrable at autopsy. In the only instance in which an x-ray of the chest was taken, the heart was not grossly enlarged. The outstanding clinical sign of myocarditis was the tachycardia, and it is our feeling that a heart rate of over 200 beats per minute in an acute infection in the newborn infant is likely to reflect myocarditis.

The disease ran its course too quickly for unequivocal evidence of congestive failure to occur, and it was not observed in the two infants who survived. The opportunity to use digitalis scarcely presented itself, nor could it have affected the outcome in the infant first seen alive, but who died in a few hours. We were impressed by the forcefulness of the heartbeat in two cases.

In the infant who survived, the contribution made by treatment with cortisone, penicillin, streptomycin, and Terramycin was difficult to assess. The same measures were employed prophylactically in one infant admitted for observation because of contact. The disease was not thereby prevented but its course was shorter and clinically much milder than the other cases, and it is possible that the drugs exercised a salutary effect.

In so far as the pathology of the heart is concerned the gross finding was a dilatation of all four chambers, the myocardium being thickened and congested. The pericardium and endocardium showed relatively slight changes. Histological study revealed severe inflammatory changes in the myocardium. There would seem to be little doubt, therefore, that the patients' clinical signs and symptoms of profound cardiac weakness and collapse resulted from the severe involvment of the heart muscle by the infective process.

It is interesting to note the histological resemblance to the so-called isolated myocarditis described by Fiedler, and to speculate whether the changes in the latter condition are not in many of the described instances due to viral infection.

In this outbreak, a Coxsackie group B type 3 virus was isolated from the feces of one of the babies who recovered. The finding of a virus in the feces does not necessarily incriminate it as the cause of the patient's illness. There are several viruses which are known to occur in association with the agent responsible for the disease, but which apparently play no causative role in the disease. For example, lesions of herpes simplex virus infection are seen frequently in cases of bacterial meningitis, pneumonia, and a number of other diseases, and Coxsackie group A virus is frequently found in association with poliomyelitis virus in cases of paralytic poliomyelitis. Nevertheless, it is now clear that Coxsackie group B virus is an important pathogen as it is the cause of Bornholm disease, and in Southern Africa is the commonest cause of benign meningoencephalitis.[5, 6] Both

these conditions were prevalent in Johannesburg at the time of the outbreak.

Bornholm disease shows a characteristic tendency for relapses to occur (Chart III), usually two and occasionally three such being noted. In these relapses the signs and symptoms of the primary illness recur. In Bornholm disease the rises and falls of temperature are characteristically sharp, with an intervening period of normal temperature.

In several of the cases in the newborn infants under discussion there

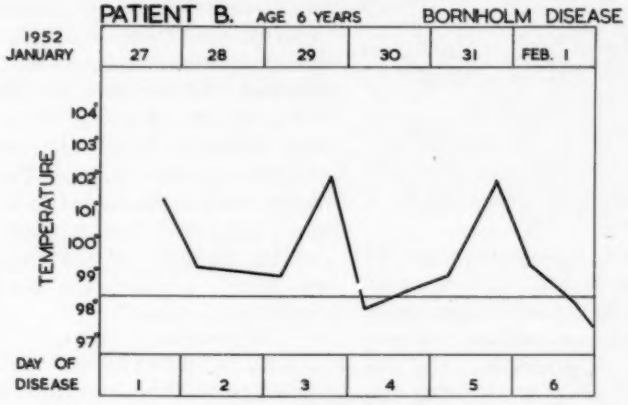

Chart III.

was a similar type of temperature chart (Charts I and II) and this tendency to recrudescence would seem to be a not uncommon feature of this illness.

It is probable that in susceptible newborn babies the infection runs a much more severe course than in susceptible adults. The lesions observed in the fatal cases in this series also recall in their characteristics those known to be caused by Coxsackie group B virus in baby mice, as, for example, the patchy myocarditis with eosinophilic degeneration of the cytoplasm and pyknotic fragmentation of the nuclei. In one patient there was also a focus of inflammation in the brain resembling that produced by Coxsackie group B virus in some baby mice.

It is significant that a woman discharged from this maternity home before the outbreak developed meningoencephalitis soon afterward. Virus studies were not carried out in her case, but considered retrospectively it seems likely that her illness was due to Coxsackie group B virus infection, and that this infection had been introduced into the maternity home about this time. Unfortunately, no serological studies were done in this outbreak as the preinfection or early acute phase specimens of blood were not available to compare with the convalescent phase specimens. However, the finding of lesions resembling those produced by Coxsackie group B virus in the fat pad and brain of baby mice inoculated with brain suspension of two fatal cases greatly strengthened the suspicion that this virus was responsible for the outbreak. Indeed it appears

that Coxsackie group B virus may cause a fatal infection in newborn human babies as it does in baby mice.

SUMMARY

In October and November, 1952, at which time Bornholm disease was prevalent in Johannesburg, a number of babies became ill while in, or soon after discharge from, the maternity home in which they were born. Their ages at onset ranged from 5 to 17 days.

Characteristically they showed a biphasic type of illness, the initial episode consisting of a few loose stools followed after an interval of three to eight days by a fulminating illness ending in a circulatory collapse. Of ten babies affected six died.

The main clinical evidence for myocarditis was a tachycardia above 200 beats per minute and abnormal T_1 in the electrocardiogram.

Post-mortem examination carried out on three of the fatal cases revealed that the outstanding lesion was a patchy myocarditis. In one case a focus of encephalitis was also demonstrated. It was concluded that death resulted from acute heart failure and circulatory collapse.

Bacteriological investigations failed to reveal a cause for this condition.

In virus studies it was shown that the baby mice inoculated with suspension of the brains from two of the fatal cases developed lesions of the brain resembling those produced by Coxsackie group B virus. Fat pad lesions resembling those produced by Coxsackie group B virus were also seen in sections of these mice, as well as in baby mice inoculated with the feces from two of the babies who recovered. One of these viruses was established in serial passage, and it regularly produced fat pad lesions. It was typed in cross-immunity tests and shown to be a Coxsackie group B type 3 virus.

It was concluded that in newborn babies Coxsackie group B virus may be a cause of an acute infection associated with a myocarditis, which may end fatally.

ADDITIONAL NOTE

Recently, Coxsackie group B virus has been isolated from the heart muscle of a newborn infant admitted to the Transvaal Memorial Hospital for Children when 9 days old. This child had symptoms and signs of myocarditis and died soon after admission.

Histological sections showed lesions of myocarditis similar to those described in this paper. This case will be fully documented in a paper to be published, but its occurrence and the isolation of the virus from the muscle confirm the conclusion drawn in this paper.

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RECTAL TEMPERATURES OF TERM NEWBORN INFANTS WITH APNEA

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A STUDY of the temperatures of newborn term infants led to the chance observation that apnea neonatorum may be accompanied by profound alterations in the rectal temperature.

PROCEDURE

Immediately following delivery the thermistor element of a Tele-thermometer[1] was inserted beyond the rectal sphincter of the newborn infant. Temperatures were then observed continuously while the baby was in the delivery room.

RESULTS

Figs. 1, 2, 3, and 4 are continuous rectal temperature records of four term infants with apnea during the period immediately following delivery. Three of the infants were delivered vaginally, and one baby was delivered by cesarean section.

The infant whose temperature curve is shown in Fig. 1 had onset of immediate, deep but irregular respirations which suddenly ceased without apparent cause five minutes after delivery. The rectal temperature rose 2.5° F. during the first minute of apnea and decreased 0.5° F. during the following two minutes of apnea. The baby was not cyanotic. Respiration was resumed after the buttocks were slapped gently once. During the first minute after respiration was resumed the temperature decreased 1.5° F., was stable for three minutes, and then gradually decreased until the infant left the delivery room, at which time the rectal temperature was 96.8° F.

Fig. 2 is the temperature curve of an infant born of a mother who had an upper respiratory infection and an oral temperature of 101.4° F. at the time of delivery. This baby's initial temperature reading was higher than that of babies born of afebrile mothers. The infant did not breathe immediately, and during the third minute of extrauterine life his temperature rose 1.4° F. The temperature decreased 0.2 F., and respiration was initiated by gentle manual stimulation. The temperature decreased 0.2° F. during the first minute of respiration and 1.0° F. the following minute. The slight rise in temperature (0.4° F.) and the sharp fall (3.3° F. during the 11- to 14-minute period of neonatal life) occurred during a period of normal shallow respiration and without any change in physical environment or somatic activity. The infant did not cry and was never cyanotic.

The infant delivered by cesarean section had a temperature of 99.2° F. (Fig. 3) two minutes after delivery. (Infants having immediate sponta-

From the Department of Obstetrics and Gynecology, Emory University School of Medicine and Grady Memorial Hospital.

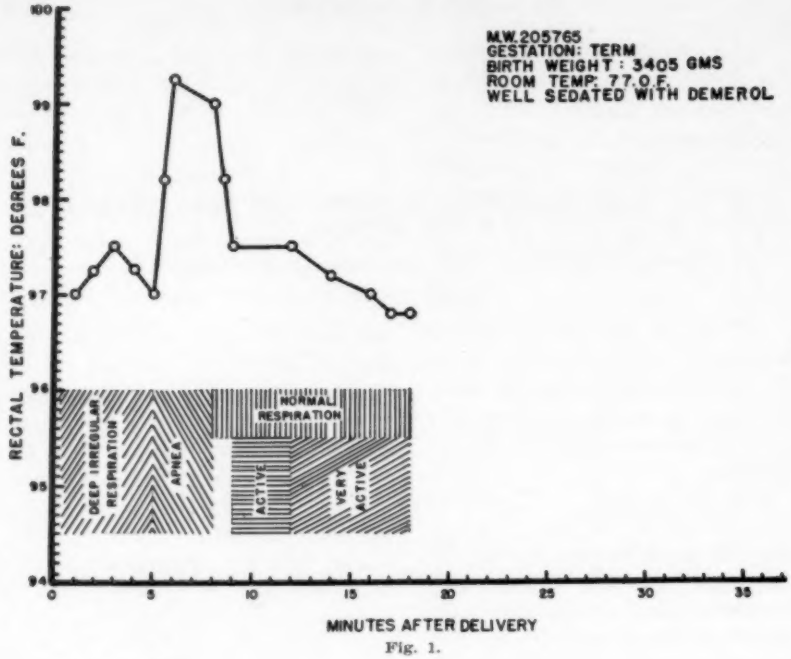
M.W. 205765
GESTATION: TERM
BIRTH WEIGHT: 3405 GMS
ROOM TEMP: 77.0 F.
WELL SEDATED WITH DEMEROL
RECTAL TEMPERATURE: DEGREES F.
100
99
98
97
96
95
94
DEEP IRREGULAR RESPIRATION
APNEA
NORMAL RESPIRATION
ACTIVE
VERY ACTIVE
0
5
10
15
20
25
30
35
MINUTES AFTER DELIVERY

Fig. 1.

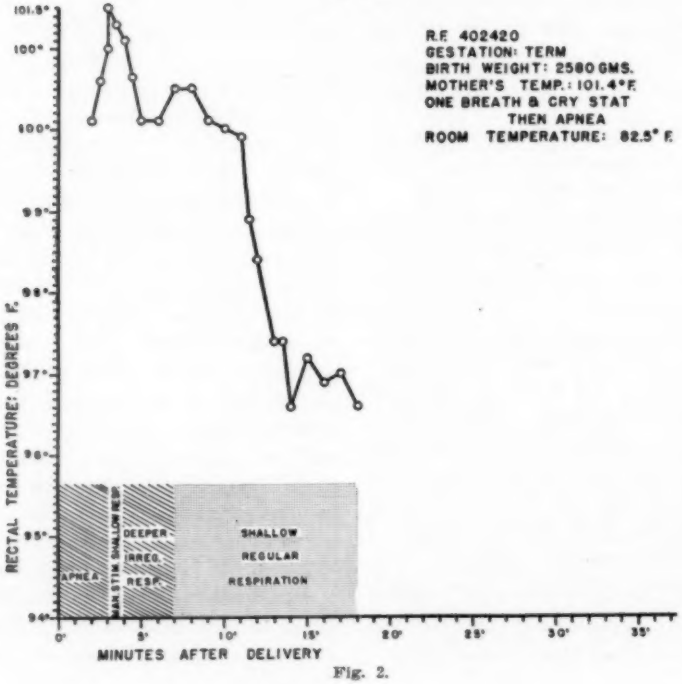
R.F. 402420
GESTATION: TERM
BIRTH WEIGHT: 2580 GMS.
MOTHER'S TEMP.: 101.4°F.
ONE BREATH & CRY STAT
THEN APNEA
ROOM TEMPERATURE: 82.5° F.
RECTAL TEMPERATURE: DEGREES F.
101.5°
100°
99°
98°
97°
96°
95°
94°
APNEA
MAINSTEM SHALLOW RESP.
DEEPER IRREG. RESP.
SHALLOW REGULAR RESPIRATION
0'
5'
10'
15'
20'
25'
30'
35'
MINUTES AFTER DELIVERY

Fig. 2.

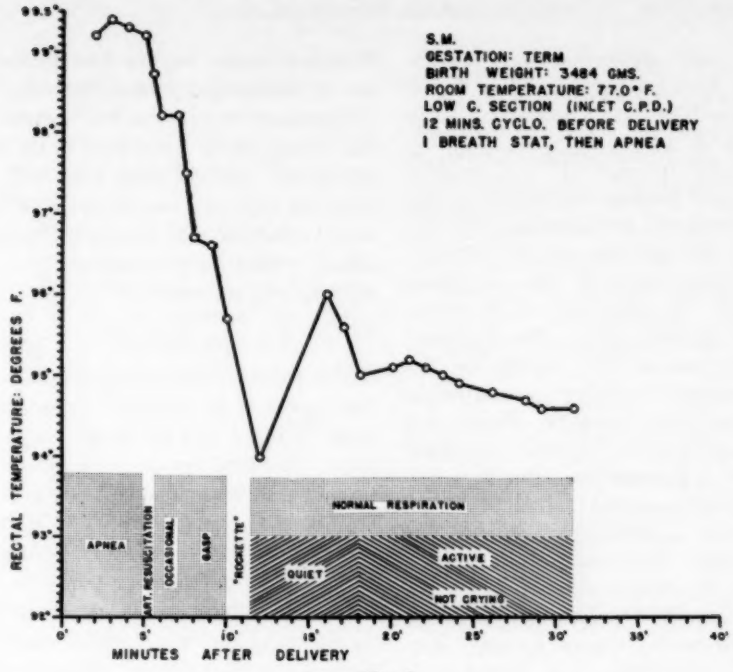
S.M.
GESTATION: TERM
BIRTH WEIGHT: 3484 GMS.
ROOM TEMPERATURE: 77.0° F.
LOW C. SECTION (INLET C.P.D.)
12 MINS. CYCLO. BEFORE DELIVERY
1 BREATH STAT, THEN APNEA
RECTAL TEMPERATURE: DEGREES F.
APNEA
GASP
"ROCKETTE"
NORMAL RESPIRATION
QUIET
ACTIVE
NOT CRYING
MINUTES AFTER DELIVERY

Fig. 3.

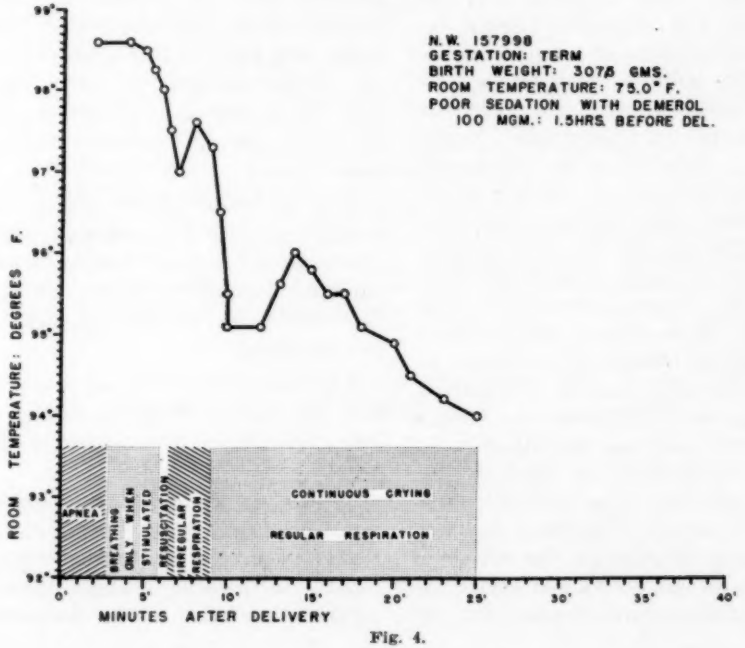
N.W. 157998
GESTATION: TERM
BIRTH WEIGHT: 3078 GMS.
ROOM TEMPERATURE: 75.0° F.
POOR SEDATION WITH DEMEROL
100 MGM.: 1.5HRS. BEFORE DEL.
ROOM TEMPERATURE: DEGREES F.
APNEA
BREATHING ONLY WHEN STIMULATED
RESUSCITATION
IRREGULAR RESPIRATION
CONTINUOUS CRYING
REGULAR RESPIRATION
MINUTES AFTER DELIVERY

Fig. 4.

neous and continuous respiration usually have temperatures 1 to 2° below this level at 2 minutes.) The baby took one breath immediately after delivery and did not breathe again until artificial resuscitation was begun with the Emerson infant resuscitator five minutes after delivery. After approximately two or three artificial respirations the infant gasped spontaneously. The temperature decreased 1.0° F. during the first minute following resuscitation, was stable for the next minute, and decreased 1.5° F. during the third minute. Respiration during this three-minute period consisted of an occasional spontaneous gasp. The temperature continued to fall rapidly, and at 10 minutes after delivery the infant ceased to gasp and was placed in a Rockette, where regular, continuous respiration was initiated in one and a half minutes, and the Rockette was stopped. During the first four minutes of regular respiration the infant's temperature rose 2.0° F. and after a rapid 1.0° decrease the temperature decreased slowly until the time when the infant was taken to the nursery. In spite of the respiratory difficulties experienced by this infant he was never cyanotic.

The first breath of the fourth baby (Fig. 4) occurred two and a half minutes after delivery and the baby had only an occasional respiration induced by mild manual stimulation. Six minutes after delivery the infant's color was poor, and the Emerson infant resuscitator was used briefly. Nine minutes after delivery, continuous, regular respiration and crying began. During the first minute of continuous respiration and crying the rectal temperature dropped 2.2° F. With no change in physical environment, respiration, somatic activity, or crying the temperature first increased and then slowly decreased until the infant left the delivery room. This baby had grunting respiration, thoracic cage retraction, and flaring of the ala nasae. The baby's course in the nursery was uneventful.

DISCUSSION

The figures demonstrate graphically that apnea of the newborn infant may cause a rapid rise in rectal temperature. The first respirations following apnea are "accompanied" by a precipitous fall (as great as 1.3° F. per 30 seconds) in temperature. Normal term infants without apnea fail to exhibit this rapid rise in temperature, apnea being the only variable; and although the "nonapneic" infant's temperature may fall rapidly, the immediate fall is of less amplitude.[2] The initial temperatures of infants who did not breathe immediately upon birth were higher than those of infants with immediate onset of continuous respiration.

It is interesting to note that of the mothers of the four apneic babies presented, one had anesthesia, one had clinically adequate sedation, one had clinically inadequate sedation, and one was unsedated.

A review of the literature failed to find any data depicting a change in body temperature with apnea in the human being.

Speculation as to the physiological signicance of these temperature changes is interesting, particularly in respect to possible changes in the oxygen dissociation curve, absorption

coefficient of oxygen, and blood pH. Of more importance, however, is any change in the quantity of oxygen ultimately available for tissue metabolism during the period under consideration.

Further study is necessary to determine whether the phenomena observed are due to physiological alterations or are pathological manifestations.

SUMMARY

Apnea of the newborn infant may be accompanied by a precipitous rise in the rectal temperature. As respiration ensues, rectal temperatures fall to normal levels.

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Greenland [New Hampshire], Oct. 3d, 1773.

The Subscriber, one of your Readers, out of good Will to Man, desire these Lines may have a Place in your next Paper.

I have been greatly affected the most of my Days by taking Poison from a Bush called Poison-Elder, or Poison-Shoemake, and other noctious Vegitives, and never could find any Thing that would give Relief quick, till of late I found that Washing the Place poisoned with Rum as soon as it begins to come out, three or four Times thoro'ly or more if need be. —It is the quickest and most absolute Cure of any Thing I ever used or heard of in my Life.

Sam'l Hinsdale

FROM BOSTON EVENING POST, OCTOBER 18, 1773.

ELECTROENCEPHALOGRAPHIC CHANGES IN CHILDREN WITH ARTIFICIALLY INDUCED HYPERTHERMIA

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MANY of the convulsions which occur in the latter part of infancy and in the first few years of childhood merely represent an initial symptom of acute febrile illness. However, several studies have indicated that a significant percentage of children who have these so-called "febrile convulsions" subsequently have spontaneous seizures.[1, 2, 3] Since approximately 6 to 8 per cent of all children have febrile convulsions,[4] it would appear desirable to be able to predict the probability of subsequent seizures in young children whose initial seizure (or seizures) occurs in relation to an acute febrile disorder. It seemed worth while to determine whether the electroencephalographic response to induced fever might differ in the child who developed convulsions with fever from that in the child who had no history of convulsions of any kind. Therefore, electroencephalographic studies have been carried out on children during hyperthermia induced by the injection of typhoid vaccine. The results indicate that all children respond similarly to fever, regardless of the previous history.

SUBJECTS

With the exception of a 2-year-old boy and a 10-year-old boy, the subjects ranged in age from 3 to 6 years. The ages of the children tend to be somewhat older than those in whom a sudden rise in temperature might be anticipated as a natural response to a disease process and in whom naturally occurring febrile convulsions are most likely.

Seven children had a history of three or more convulsions with fever; three had no family or personal history of convulsions of any kind; one had a history of a previously abnormal electroencephalogram; and one (W. S.) whose twin brother (J. S.) had had febrile convulsions (included in this study) had no history of seizures. A set of identical twins (D. C. and M. C.) and their older brother (R. C.) are included in the series. Preliminary electroencephalograms were normal in all of the children.

METHOD

Hyperthermia was produced by the intravenous administration of 1 c.c. of a typhoid vaccine containing 100 million organisms per cubic centimeter; the same dose was given to all subjects regardless of age. Previous experience indicated the likelihood of a rise in temperature above 103° F. with this dose.

All electroencephalographic recordings were made on a six-channel Grass Model IIID machine. Bentonite paste

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was used to secure the eight scalp electrodes (frontal, parietal, occipital, and temporal). A skin resistance of less than 20,000 ohms was considered satisfactory, but resistances usually averaged 10,000 ohms or less. Electrodes were replaced as necessary. At least one tracing was secured prior to the day of the test in order to obtain "awake but quiet," "going to sleep," and "asleep" records for each child. Preliminary sedation, using bulbocapnine 5 mg. per kilogram of body weight, was necessary in order to obtain satisfactory records on twins D. C. and M. C.[5] Following administration of the typhoid vaccine, continuous tracings were obtained. After the entire record had been analyzed, representative samples were cut out at

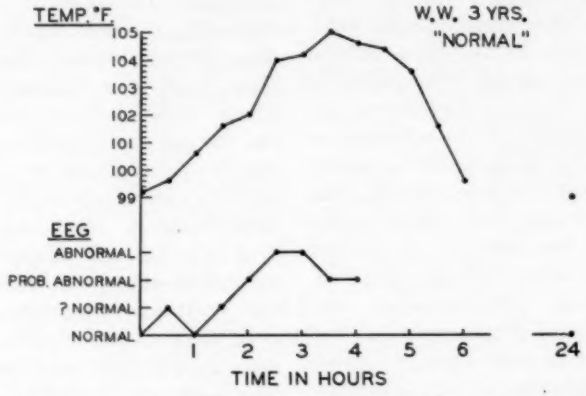

Fig. 1.—This graph summarizes the findings in W. W., a 3-year-old male with no personal or family history of convulsions (Table I, No. 10). The upper portion of the graph represents the temperature curve following the intravenous administration of typhoid vaccine. The lower portion shows the progression of electroencephalographic abnormalities as the temperature rises. The electroencephalograph returned to normal within twenty-four hours.

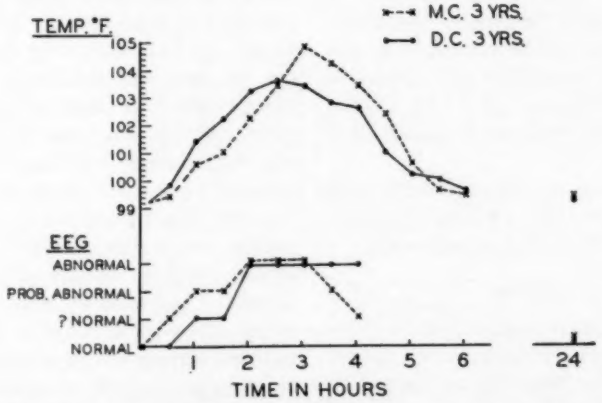

Fig. 2.—This graph summarizes the findings in M. C. and D. C., 3-year-old monozygotic twin females, both of whom had personal and family histories of convulsions with fever. A comparison with Fig. 1 shows no significant difference in the electroencephalographic response to induced fever, despite the previous occurrence of convulsions.

"half-hour" intervals; these samples were classified as normal, probably normal, probably abnormal, or abnormal, and the results were charted against a record of the temperature (Figs. 1 and 2).

Rectal temperatures were recorded every 30 minutes, unless the appearance of the child warranted more frequent observations. One of the authors remained in attendance from the time of injection of typhoid vaccine until the temperature had begun a definite return toward normal. The child was allowed water by mouth as desired but no attempt was made to encourage a high intake of fluids until the study was completed. Aspirin (60 mg. per year of age) was given orally or rectally when the temperature reached 104° F., or when definite electroencephalographic abnormalities appeared. Sodium phenobarbital (5 mg. per kilogram of body weight) was administered intramuscularly, if convulsions occurred or seemed imminent. One child (R. C.) was given sodium phenobarbital intramuscularly at the time of the intravenous injection of typhoid vaccine, because he had a history of many febrile convulsions, and because our experience with previous patients indicated that he would have marked electroencephalographic changes.

After the test electroencephalograms were obtained daily until all evidences of abnormalities had disappeared.

RESULTS

The results are summarized in Table I. Maximum temperatures ranged from 102° to 105.6° F. and were attained by all subjects between two and three and one-half hours after the injection of typhoid vaccine. Subjective complaints consisted of stiff neck and back, headache, and malaise. Restlessness, chills, nausea, and vomiting were common. As the temperature increased, the children became quiet, but seldom slept.

Abnormalities were observed in the electroencephalograms of all the children and occurred in all but one before the maximum elevation of temperature. The changes consisted of high-voltage, slow waves, increased delta activity, spike-and-wave formations, and some seizure discharges. Three clinical convulsions occurred, two in the group with a history of febrile seizures, and one in the boy with the previously abnormal electroencephalogram; these responded promptly to the administration of sodium phenobarbital intramuscularly. The electroencephalograms of all children were normal within three days and usually were so within twenty-four hours.

DISCUSSION

The possibility exists that the electroencephalographic changes observed were due to some factor other than the fever. As pointed out by Greenblatt,[6] the changes are the same, although more marked, as those induced by hyperventilation. Krakau and Nyman[7] also have suggested that fluid loss, acidosis, or other changes accompanying the rise in temperature may be partly responsible for the electroencephalographic abnormalities. The plasma CO_2 content and pH were within the normal range in one of our patients during the occurrence of electroencephalographic changes. It does not seem likely that any of the factors cited except hyperthermia could have been present in our patients in suf-

TABLE I

NAME	AGE (YR.)	DIAGNOSIS	MAX. TEMP.		EEG ABNORMAL		CONVULSIONS	EEG RETURNED TO NORMAL BY
			T° F.	TIME	T° F.	TIME		
1. W. H.	3 ♂	Pulm. tbc.	104.0°	3½ hr.	104.0°	3½ hr.	No	4 hr.
2. J. S.	3 ♂	Febrile convulsions	103.0°	2 hr.	102.2°	1½ hr.	No	1 da.
3. W. S.	3 ♂	Well child	105.6°	2 hr.	103.2°	1½ hr.	No	1 da.
4. C. R.	4 ♀	Febrile and psychomotor	104.6°	3 hr.	101.0°	1 hr.	Yes (2½ hr., 104°)	6 hr.
5. M. C.	3 ♀	Febrile convulsions	105.0°	3 hr.	102.0°	2 hr.	No	1 da.
6. D. C.	3 ♀	Febrile convulsions	104.0°	2½ hr.	103.0°	2 hr.	No	1 da.
7. R. C.*	6 ♂	Febrile convulsions; Grand Mal	105.2°	3½ hr.	102.0°	1½ hr.	No	1 da.
8. I. G.	5 ♀	Febrile convulsions	103.8°	3 hr.	99.2°	2½ hr.	Yes (4½ hr., 103°)	3 da.
9. S. H.	2 ♂	Febrile convulsions	103.0°	2½ hr.	103.0°	2½ hr.	No	1 da.
10. W. W.	3 ♂	Social problem; pneumothorax	105.0°	3½ hr.	104.0°	3 hr.	No	1 da.
11. J. F.	10 ♂	History of abnormal EEG 3 yrs. ago	104.0°	3½ hr.	103.2°	2½ hr.	Yes (3 hr., 104°)	3 da.
12. C. W.	6 ♂	Hemihypertrophy	102.0°	2½ hr.	101.6°	2 hr.	No	1 da.

*Phenobarbital (5 mg./kg. of body weight) given intramuscularly at the time of the intravenous injection of typhoid vaccine.

ficient degree to cause significant electroencephalographic abnormalities.

Most investigators[7, 8] have found increased delta activity, slowing and some spike-and-wave activity in adults during artificial hyperthermia. Hoagland,[9] however, reported only increased beta activity. These electroencephalographic changes are the same whether the fever is induced by malaria, typhoid vaccine, or inductothermy.[10] All of the reported cases had disease of the central nervous system, so that it can only be inferred that the electroencephalogram of a normal adult would show similar changes.

Livingston[11] has demonstrated that the electroencephalograms of some children with naturally occurring fever contain high-voltage slow waves for at least three days after the children became afebrile. Our observations on children with febrile illnesses are in line with those of Livingston. For these reasons caution is indicated in interpreting abnormal electroencephalograms as being indicative of disease of the central nervous system when these abnormalities are associated with a recent fever. These observations tend to minimize the significance of Lennox's[1] interpretations of persistent electroencephalographic abnormalities following febrile convulsions, since children without convulsions but with a febrile illness might show similar results.*

*This finding helps to explain results obtained in an unpublished study by one of the authors (H.W.B.). Several years ago an attempt was made to secure data on the incidence of febrile convulsions in the patients admitted to St. Christopher's Hospital for Children, and on the frequency of abnormal electroencephalograms in patients with a personal or familial history of febrile convulsions. A surprising number of these children had abnormal electroencephalograms, but it now seems apparent that febrile illnesses responsible for the hospital admission were responsible for at least some of the changes observed.

The recent report of Lennox, Sibley, and Zimmerman[12] of febrile convulsions in kittens associated with induced fever suggested our study in children. In view of the height and duration of the fever induced in their kittens, it is not surprising that anatomical and electrical cerebral changes were produced. It remains an assumption, however, that the common form of febrile convulsions, with its associated *reversible* electroencephalographic changes, produces *irreversible* brain damage.[13] Nevertheless, data such as those presented by Lennox and her associates made us unwilling to continue this study, because of the marked electroencephalographic changes produced.

Cerebral activation sufficient to elicit electrographic seizure discharges in persons with a history of seizures but without electrographic abnormalities is occasionally desirable as a diagnostic measure. Many methods of activation have been suggested (sleep, photic driving, hyperventilation, insulin, and Metrazol). The ideal method would be one which produced no changes in normal patients but always produced seizure discharges directly proportional to the current or future clinical state of the abnormal patient. Induced fever as employed in the present series is worthless in distinguishing children with convulsive disorders from those without such tendencies.

Why some children convulse with a fever and others do not remains a mystery. Results of this study indicate that all children with high fevers should receive sufficient amounts of fluids, antipyretics and sedation, and of antibiotics when indicated, whether or not the child has a history of convulsions when febrile.

SUMMARY

1. The electroencephalographs of twelve children were recorded following the intravenous administration of typhoid vaccine.

2. Seven children had a history of three or more convulsions with fever; three had no family or personal history of convulsions of any kind; one had a history of a previously abnormal electroencephalogram; and one had a twin brother who had febrile convulsions.

3. Electroencephalographic changes consisting of high-voltage slow waves, increase delta activity, spike-and-wave formations, and some seizure discharges occurred in all tracings.

4. The fact that otherwise normal children have electroencephalographic changes during and shortly after a febrile episode without convulsions should be considered in the interpretation of electroencephalographic changes following a febrile convulsion.

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RETROLENTAL FIBROPLASIA

Influence of Reduced Electrolyte Intake on the Incidence and Severity of the Disease

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IN MOST premature units cow's milk mixtures have replaced human milk for routine feeding. The mineral content of cow's milk is greater than that of human milk. Because of the suspected physiologic limitations of premature infants, the higher mineral content of cow's than of human milk may be sufficient to overload the metabolic capacities of some premature infants.[1, 2] Electrolyte overloading produces edema and vascular disturbances which have been suggested to be precipitating factors of acute retrolental fibroplasia (RLF).[3a] One of the authors (R. H.) has previously reported the incidence of complete blindness due to RLF in infants born weighing less than 1,501 grams to be 44 per cent (twenty-one of forty-eight infants) when cow's milk formulas with 0.2 Gm. per 100 ml. added sodium chloride were offered ad libitum.[3b] The current study was made to investigate the corollary of the previous observation: since increased electrolyte load was thought to be associated with increased incidence of RLF, reduced electrolyte load may reduce the incidence of RLF.

This study reports the incidence and severity of acute RLF in premature infants fed from birth one of two types of feedings. The experimental feedings had the electrolyte content of human milk. Part of the infants received human milk, and part an experimental formula. The control formula had the electrolyte content of cow's milk mixtures in common use. The carbohydrate, protein and fat contents of the two formulas were identical (Table I).

DESIGN OF STUDY

Patients.—One hundred forty-two infants, all weighing 1,700 grams or less at birth, were included in the series. These infants were resident in the University of Texas Nursery, Jefferson Davis Hospital Nursery, and three private nurseries in Houston (Hermann Hospital, Memorial Hospital, and St. Joseph's Hospital) (Table II).

In the private nurseries the infants were under the care of private physicians cooperating with the authors.

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Work done in the premature units of the Children's Hospital, Galveston; Jefferson Davis City-County Hospital, Hermann Hospital, Memorial Hospital, and St. Joseph's Hospital, Houston, Texas.

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1. *University of Texas and Jefferson Davis Hospital:* Infants were grouped according to birth weight and paired as well as possible by weight, sex, and color. One of each pair was given the control formula from birth and the other the experimental formula (Table I). All infants were given nothing by mouth for twenty-four hours, followed by 5 per cent glucose in water for twenty-four hours. (In infants with edema or respiratory difficulty, oral feedings were withheld over a longer period.) On the third day a dilute formula mixture, and between the seventh and tenth day a full formula (120 cal. per kilogram and 160 ml. per kilogram per twenty-four hours), was offered. After the tenth day intake was calculated to 120 cal. and 160 ml. fluid per kilogram per twenty-four hours until the patients weighed 2,000 grams. At that time infants without evidence of RLF were fed a mixture of 8 ounces evaporated milk, 16 ounces water, and 4 tablespoons Dextri-Maltose (for five days) until weight reached 2,500 grams, and then sent home. Infants with RLF were treated individually. Except for the formulas all infants were managed in similar manner. Iron was not given. Blood transfusions were rarely used, and then in volumes of less than 5 ml. per kilogram. Multivitamins (Poly-Vi-Sol) were given daily, beginning the first week of age. Oxygen was controlled by limitation of its use to definite indications.

Seventy-eight per cent of these infants were of the Negro race.

2. *Private Nurseries:* One of each pair of infants in the various private nurseries was given one of the proprietary milk formulas (Table II) and the other his own mother's milk. Infants offered more than one type of feeding were excluded from the study group. In this group of private patients, neither fluid nor caloric intake was standardized. Intakes recorded in the hospital records of these infants were found in retrospect rarely to exceed 120 cal. and 160 ml. per kilogram of body weight per day.

TABLE I

	GM./100 ML.			MEQ./LITER						CAL./
	PRO.	FAT	COH	NA	K	CL	CA	P	MG.	LITER
Unmodified cow's milk	3.3	3.8	4.6	25.0	35	28	63	64.0	10.8	666
Pooled mature human milk	1.25	3.8	7.0	6.5	14	12	17	10.4	3.3	670
Control formula*	2.85	2.9	9.4	23.0	30	24	54	54.0	9.0	750
Experimental formula	2.85	2.9	9.4	5.0	14	15	30	23.0	3.3	750

*Whole cow's milk mixtures plus 5 per cent Dextri-Maltose No. 2.

TABLE II

	JEFFERSON DAVIS HOSPITAL AND UNIVERSITY OF TEXAS	PRIVATE CASES
Race	Predominantly Negro 78%	All white
Low electrolyte formula	Experimental formula	Human milk
Control formula	Similar to above in fat, protein, and carbohydrate, with unadjusted mineral content	Various proprietary formulas (Olac, Dalactum, Similac, Bremil)

These infants were all of the white race.

Examination and Classification.—Eyes were examined ophthalmoscopically after atropine or homatropine and Neo-Synephrine dilation at weekly intervals until the patient's discharge at weight of 2,500 grams from the various premature units. All patients with RLF were examined by two or more experienced observers.

TABLE III. INCIDENCE OF ACUTE RLF IN PREMATURE BABIES FED FROM BIRTH WITH CONTROL, EXPERIMENTAL, OR HUMAN MILK

	BIRTH WT. IN GRAMS	NORMAL	RLF	TOTAL	% RLF	NORMAL	RLF	TOTAL	% RLF
		EXPERIMENTAL FORMULA				CONTROL FORMULA			
J. D. H. (intake calculated to 120 cal./kg., predominantly Negro)	1,501-1,700	18	5	23	22	13	2	15	13
	1,001-1,500	14	6	20	30	16	5	21	24
	Less than 1,000	0	1	1	100	1	3	4	75
	Total	32	12	44	27	30	10	40	25
U. of T. (intake calculated to 120 cal./kg., predominantly Negro	1,001-1,500	3	1	4	20	2	3	5	60
	Less than 1,000	1	0	1	0				
	Total	4	1	5	20	2	3	5	60
		HUMAN MILK				FORMULA			
Private nurseries (intake not calculated, all white infants)	1,501-1,700	3	3	6	50	4	2	6	33
	1,001-1,500	8	8	16	50	2	7	9	78
	Less than 1,000	3	4	7	57	2	2	4	50
	Total	14	15	29	52	8	11	19	58
Total	1,501-1,700	21	8	29	28	17	4	21	19
	1,001-1,500	25	15	40	38	20	15	35	43
	Less than 1,000	4	5	9	56	3	5	8	62
	Total	50	28	78	36	40	24	64	37

In seventy-eight babies of birth weight 1,700 grams or less, fed human milk or experimental formula, RLF developed in twenty-eight, or 36 per cent. In sixty-four infants of similar birth weight fed control formula, twenty-four, or 37 per cent, developed RLF.

Conclusion: The incidence of acute RLF is approximately the same in both groups.

TABLE IV. INCIDENCE OF SEVERE AND MILD RLF IN PREMATURE INFANTS FED FROM BIRTH WITH EXPERIMENTAL FORMULA, HUMAN MILK, OR CONTROL FORMULA
1952-1953

	BIRTH WT. IN GRAMS	MILD RLF	SEVERE RLF	TOTAL RLF	% SEVERE RLF	MILD RLF	SEVERE RLF	TOTAL RLF	% SEVERE RLF
		EXPERIMENTAL FORMULA				CONTROL FORMULA			
J. D. H. and U. of T. nurseries	1,501-1,700	5	0	5	0	1	1	2	50
	1,001-1,500	4	3	7	44	3	5	8	62
	Less than 1,000	0	1	1	100	1	2	3	67
	Total	9	4	13	31	5	8	13	61
		HUMAN MILK				FORMULA			
Private nurseries	1,501-1,700	2	1	3	33	1	1	2	50
	1,001-1,500	3	5	8	63	3	4	7	57
	Less than 1,000	3	1	4	25	2	0	2	0
	Total	8	7	15	47	6	5	11	45
Total	1,501-1,700	7	1	8	13	2	2	4	50
	1,001-1,500	7	8	15	55	6	9	15	66
	Less than 1,000	3	2	5	40	3	2	5	40
	Total	17	11	28	39	11	13	24	54

In twenty-eight with RLF fed with human milk or experimental formula, ten, or 39 per cent, were classified as severe (Grades III to V). In twenty-six infants with RLF fed with the control formula, thirteen, or 50 per cent, were classified as severe.

Conclusion: The incidence of severe RLF is not significantly different in the two groups.

The stages of disease found were classified according to the definitions of the National Committee for the Prevention of Blindness.[4] Disease was considered mild if it never advanced beyond stage I or II, and severe if advanced to stages III to V at any time.

RESULTS

One hundred forty-two premature infants weighing less than 1,701 grams at birth were studied. The total incidence of acute RLF was 36 per cent. The sample is large enough to permit valid conclusions. This incidence of acute RLF is consistent with the experience of others.[5]

Incidence of RLF.—The incidence of acute RLF in the Jefferson Davis City-County Hospital and University of Texas was 29 per cent (thirteen of forty-five) for those fed the control mixture, and was 27 per cent (thirteen of forty-nine) for those fed the experimental mixture. The incidence of acute RLF in the private nursery infants was 58 per cent (eleven of nineteen) for those fed proprietary formulas and 52 per cent (fifteen of twenty-nine) for those fed human milk (Table III).

Severity of Acute RLF.—To determine whether or not low electrolyte intake from birth might alter the severity of acute RLF, the patients with RLF in each group were tabulated and classified according to severity of disease. Acute RLF, not progressing beyond stage I or II, was designated "mild," while acute RLF, stages III to V, was designated as "severe."[4]

Of infants with acute RLF, 39 per cent (eleven of twenty-eight) given low electrolyte feedings (human milk or experimental formula) had severe RLF, while 54 per cent (thirteen of twenty-four) given control formula had severe RLF (Table IV). This difference is not significant. By a null hypothesis, $X^2 = 1.15$, P is greater than 0.20.

DISCUSSION

The incidence of acute RLF in the combined University of Texas and Jefferson Davis Hospital group is lower than in the combined private nurseries. This difference is related to previously observed racial differences and susceptibility to the process.[6] White infants in the University of Texas and Jefferson Davis Hospital nurseries have a similar incidence of acute RLF to that found in the private nurseries. The greater maturity of the vascular structures of the eyes of small Negro infants than of white infants of similar size and gestation in effect reduces the susceptibility of the population to RLF and accounts for the differing incidence of RLF in the two large groups studied here.

At the inception of this study, the plan was to compare the incidence of RLF in a cow's milk-fed with a human-fed population otherwise managed similarly. The practical difficulty of locating enough human milk to feed more than a limited number of infants was severe. Therefore, modification of electrolyte content of cow's milk was devised as a substitute. The similarity of results of the two experimental groups when compared with their proper controls supports the conclusions.

No apparent differences in physical growth or clinical well-being were found in the combined Jefferson Davis Hospital and University of Texas infants, whether fed the experimental cow's milk mixture or the control formula.

CONCLUSIONS

Neither the incidence nor the severity of acute RLF are decreased significantly by feeding from birth either human milk or cow's milk mixtures with electrolytes adjusted to human milk levels.

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THE INCIDENCE OF MILK ALLERGY IN PEDIATRIC PRACTICE

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THE literature contains many reports of allergic reactions to cow's milk. Some illnesses such as diarrhea or eczema are commonly attributed to allergy to cow's milk; some such as Henoch-Schönlein purpura rarely to the same thing. There are reports in the literature indicating cow's milk as the sole or primary cause of the following clinical syndromes: eczema, urticaria, angioneurotic edema, Henoch-Schönlein purpura, diaper rash, circumoral pallor, pylorospasm, colic, vomiting, diarrhea, constipation, anorexia, hematemesis, flatus, abdominal pain, refusal of milk, mucus in the stools, melena, celiac syndrome, eructation of gas, ulcerative colitis, regional enteritis, cough, croup, choking, gagging, excess mucus in the throat, chronic nasal discharge, sneezing, nasal itching or rubbing, asthma, fever, frequency, enuresis, hematuria, general irritability, convulsions, headache, nervous storms, migraine, severe behavior disturbances, excessive crying, excessive sweating, toxemia, apathy, listlessness, cyanosis, collapse, and fatal and nonfatal anaphylactic shock.

Although it is relatively easy to assess these symptoms as being due to allergy to cow's milk from a review of the case reports, difficulty arises when one attempts to evaluate the incidence. The incidence of allergy to cow's milk is obviously of considerable importance to the practicing pediatrician. Is it so rare that he will never have a case in his practice or is it so common that he must consider it in every patient he sees? The purpose of this paper is to arrive at as fair an appraisal as possible of the incidence of allergy to cow's milk in a general pediatric practice.

The cases under discussion consist of 3,000 office patients seen in my private pediatric practice. These vary in age from birth to the fifteenth birthday. Many have been followed from birth, many seen and followed from a few months of age, and many seen only as older children. Most attend the office regularly for well-child care, many come only occasionally when ill. In other words, this series consists of 3,000 patients making up the usual office population of a practicing pediatrician and are consecutive patients with the following exceptions: (1) All patients seen at any time for major allergy are excluded since there is an undue proportion of these in my practice. (2) All consultation cases are excluded if it was suspected that the referring doctor sent the patient because he thought he might be allergic since there is an undue proportion of these in my practice. (3) All patients who came directly to the office where the mother considered the child aller-

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gic were also excluded since this would also give an unfair weighting toward allergy.

This series of cases has certain defects which will influence the incidence of milk allergy discovered. (1) Exclusion of the three groups of cases listed above lowers the reported incidence since the practicing pediatrician will have many cases of major allergy and a few cases which fall into the other two groups. This is compensated for by the fact that in these three groups of cases the pediatrician should always think of milk allergy and the reported incidence will therefore apply to the "hidden" cases of milk allergy which the pediatrician must ferret out for himself. (2) The almost routine use of evaporated milk in my practice prevents an inestimable number of infants from showing symptoms of milk sensitivity since, as has been shown by Ratner,[1] the method of preparation of evaporated milk denatures it. Evaporated milk is therefore well tolerated by infants who exhibit only mild milk allergy. No estimate can be made of how often this prevents development of allergic symptoms. (3) Some of the patients were not seen until later childhood and therefore it was impossible to evaluate whether they had been allergic to milk in early life. (4) Many of the babies were breast fed entirely for the first few months of life and thus were not exposed to cow's milk during that time.

The diagnosis in each case has been made on clinical grounds alone. The patient has presented with symptoms to explain which milk allergy was suspected. Removal of all milk from the diet produced complete remission of symptoms. On at least one occasion milk added to the diet produced the same symptoms which disappeared when milk was withdrawn again.

In the 3,000 cases only nine cases of definite milk allergy were discovered, giving an incident of 0.3 per cent. The case reports follow.

CASE REPORTS

CASE 1.—B. J., vomiting.

This infant was seen at 4 months of age. At this time there was a history of her having been on evaporated milk since birth but this was vomited repeatedly one-half hour after the feeding. This had been changed to a whole milk formula which was vomited in the same manner. Solids were taken and retained. On examination, the infant appeared thin and dystrophic, with practically no subcutaneous tissue. At this time, on suspicion that she had a milk allergy, she was put on Mull-Soy. She immediately began to take this very well, with no vomiting at all, and began to gain weight. A brief trial of cow's milk shortly before 5 months of age again resulted in vomiting. At the age of 5 months she weighed 11 pounds, looked much better and was a much happier baby. She has not been observed since that time.

Comment.—This infant had a prolonged history of vomiting on cow's milk formulas. This responded dramatically to substitution of Mull-Soy for milk, returned when milk was given again, and disappeared when Mull-Soy was restarted.

CASE 2.—L. C., vomiting.

This infant was first observed at 6 weeks of age at which time there was a history that although he had done well on the breast he had been weaned at 2 weeks of age. He was then put, in turn, on partially skimmed evaporated milk, lactic acid milk, skim milk, and evaporated milk, but on each of these formulas he vomited a great deal after each feeding. The stools were normal. Physical examination was essentially negative. On the basis of the diagnosis of possible milk allergy he was put on a formula of Mull-Soy and the vomiting stopped within

twenty-four hours. He continued to take the formula well and gained weight. At 2½ months of age the milk formula again caused vomiting and Mull-Soy was substituted. At 3 months of age, because he seemed to be doing well, he was again tried on evaporated milk, starting with small quantities which were gradually increased as the Mull-Soy was reduced and two weeks later he was taking an evaporated milk formula very well. When he was last seen at 5 months of age he was off Mull-Soy and was also receiving cereal without symptoms.

Comment.—This infant had repeated vomiting on 4 different cow's milk formulas but retained Mull-Soy very well. The milk formula subsequently produced vomiting again. At 3 months he was gradually changed to an evaporated milk formula without symptoms. This indicates that cow's milk allergy may be of relatively short duration.

CASE 3.—C. B., diarrhea and colic.

This infant, first seen at the age of 1 month, had suffered from diarrhea and colic from birth and was having from four to six loose stools daily when he was discharged from the newborn nursery at 9 days of age. At this time he was on a lactic acid milk formula. The diarrhea continued in spite of changes in formula. No parenteral infection was present. Weight gain was slow. At 1 month of age he was admitted to hospital because of severe dehydration which required intravenous fluids. No pathogenic organisms were cultured from the stools. Because the diarrhea persisted and became worse when milk was reintroduced into the formula, the feeding was changed to Mull-Soy, with rapid improvement. The infant remained on Mull-Soy until he was 3 months of age at which time he was put back on skim milk. Immediately the diarrhea returned and again hospital admission was necessary because of dehydration, even though only a few milk feedings were given. The infant was again discharged on a Mull-Soy feeding. A few weeks later just 1 ounce of skim milk was added to the feeding daily with the immediate return of diarrhea. When the infant was last seen at 5 months of age he was still on Mull-Soy with added solids and was doing well, gaining well, with no diarrhea.

Comment.—This case represents one who suffered from milk allergy characterized by diarrhea, colic, and poor weight gain from birth. The clue to the diagnosis is the appearance of diarrhea on a milk formula, no pathogenic organisms being cultured from the stool, no parenteral infection being present, and no other cause of the diarrhea being found. The diarrhea responded to elimination of milk in the diet and on two occasions returned when milk was added to the diet, to clear again when milk was removed from the diet.

CASE 4.—R. B., diarrhea, buttocks rash.

This infant was first seen at the age of 3 months with a history of diarrhea. He had been on a partially skimmed evaporated milk formula since birth and had had diarrhea varying in severity associated with a severe diaper rash and at one time had been admitted to hospital because of gastroenteritis. He was discharged from hospital at 2½ months of age with a diagnosis of milk allergy on a formula of Mull-Soy. He was much improved on this formula. At 4 months of age he was doing extremely well on the diet of Mull-Soy and rice cereal. At this time he was put back on a formula of evaporated milk but immediately the buttocks rash and the diarrhea reappeared. These cleared spontaneously as soon as he was taken off the milk formula and put back on the Mull-Soy. Vegetables were started but also caused diarrhea and had to be discontinued. At 4½ months of age, because the stools were large and irritating on Mull-Soy, a meat-milk formula made with lamb was substituted. As soon as this preparation was started, the stools definitely improved and the buttocks again cleared. He was continued on the meat-milk, which was

gradually increased in quantity, and gained well. At the age of 6½ months he was a contented baby and at that time was also receiving rice or barley cereal mixed with water and a vitamin supplement.

Comment.—This infant suffered prolonged diarrhea and buttocks rash which responded promptly to the substitution of Mull-Soy for milk. Evaporated milk subsequently caused return of these symptoms which again cleared with withdrawal of milk.

CASE 5.—L. D., melena, diarrhea, celiac syndrome.

This infant was first seen at 2 weeks of age with a complaint of repeated regurgitation of whole milk formula. These symptoms continued in spite of sedation, and at 6 weeks of age the infant passed watery stools, on two occasions followed by bright blood for which no local cause could be found on physical examination. After the diarrhea had persisted for three days the infant was admitted to hospital at which time blood studies, stool cultures, barium enema, and sigmoidoscopic examination were all normal. The infant was discharged on a skim milk formula. Two days later the diarrhea recurred and there were ten to fifteen loose stools daily, although no more blood was present. The diarrhea was improved somewhat with the use of medication and a powdered skim milk feeding. At the age of 4 months there was occasionally some blood in the stools although the diarrhea was mild. Vegetables were added at 4½ months and the diarrhea became worse so they were discontinued. The diarrhea then was not much of a problem although there were frequent stools. However, at 9½ months the infant was having 8 to 9 large stools daily that were foul-smelling. The abdomen was somewhat prominent and the buttocks wasted. A tentative diagnosis of celiac syndrome possibly due to milk allergy was made and milk was removed from the diet, a milk substitute made with lamb being used in its place. As soon as this diet was started the diarrhea stopped and the stools returned to normal consistency and color. There were temporary exacerbations of the diarrhea when various solids were added to the diet but this cleared as soon as these solids were removed from the diet. The infant was fed with those solids which he would tolerate without diarrhea and the lamb formula. With this regime he continued to do well, began to gain weight rapidly, and at 20 months, when he was last seen, he weighed 23½ pounds and physical examination was negative. He was receiving the lamb formula, rice cereal, Mull-Soy, a water-soluble vitamin supplement and additional vitamin B.

Comment.—That this case is one of milk allergy characterized by melena, diarrhea, and celiac syndrome is apparent from the negative investigation for the melena and the close correlation of these findings with the administration of milk in the diet and correction of these symptoms when milk was removed from the diet. There are other factors operating as there are many solids which the infant cannot tolerate but from observation of this patient it is apparent that milk is the chief factor, most of the symptoms having developed when only milk was being given.

CASE 6.—P. D., diarrhea.

This infant, a sibling of L. D., was placed on an evaporated milk formula at birth and immediately began to have six watery stools daily. There was also considerable regurgitation of feedings. A change in formula to powdered skim milk produced no change in the clinical picture. Immediately the feeding was changed to Mull-Soy at 5 weeks of age and the diarrhea disappeared. During the next month evaporated milk was given again on two occasions, each time with the recurrence of the diarrhea. At 3 months rice and barley cereal were added but caused diarrhea and had to be discontinued. He continued to do well on only Mull-Soy with an added vitamin supplement until 5 months of age. At this time

lamb was added to the diet and was well tolerated. At 6 months of age he suffered an acute upper respiratory infection with severe cough and vomiting, necessitating admission to hospital. This apparently responded well to antibiotics but he continued to be listless and began to refuse the Mull-Soy and to vomit it. A meat formula made with lamb was substituted and was taken well for several days, then it, too, was refused and vomited. At 6¾ months of age he was admitted to hospital again in a severe state of shock. He was an ashen gray color with cold, clammy skin, rapid heart rate, very slow respirations, and was unresponsive to stimuli. Serum pH, CO_2 combining power, sodium, chloride, potassium, blood urea nitrogen, and blood sugar were all normal. In spite of treatment with Adrenalin, intravenous compound F, blood transfusions, intravenous fluids, and general supportive measures, the patient died several hours later without showing any improvement. Autopsy in the gross revealed only a generalized edema which could be accounted for by the intravenous fluids running until the time of death. Microscopic examination revealed only a minimal bronchopneumonia in the right lung although postmortem culture of the lungs was sterile. In retrospect one cannot help wondering whether this infant, allergic to cow's milk at birth, successively became allergic to the Mull-Soy and then to the lamb formula and died in acute anaphylactic shock.

Comment.—This infant suffered diarrhea from birth on an evaporated milk formula. He tolerated Mull-Soy well for several months though trials of evaporated milk still caused diarrhea, then began to refuse and vomit it. A lamb formula was then well tolerated but then he began to refuse and vomit it and died in shock, questionably anaphylactic in nature.

CASE 7.—C. L., celiac syndrome.

This infant was first seen at 18 days of age, at which time she was on the breast. The course was quite uneventful. Solids were added at the usual time without any difficulty except that she did not tolerate egg. At 12 months of age she weighed 21 pounds and at this time began to have two to three loose stools daily which did not respond to removal of all foods from the diet except powdered skim milk. Shortly after this she was observed to have a large abdomen and wasted buttocks and was put on a high protein diet with skim milk curds, lean bacon, chicken, lamb, beef, liver, cream cheese, and applesauce. There was some improvement on this regime, although some of the solids were not well tolerated. The stools became fewer in number but she continued to have two to three large loose stools daily. At 17 months of age, because of her lack of improvement and negligible weight gains since 1 year of age, milk was removed from the diet, a lamb formula being substituted, and there was immediate improvement. With continuation of the milk-free diet there was no diarrhea and the infant did extremely well. Solids were slowly added to the diet. Since some of these made the stools loose again the mother became dissatisfied and for this reason the infant was admitted to hospital for investigation at 22 months of age. Physical examination at this time was essentially negative. Stool culture was negative. The glucose tolerance test revealed a fasting level of 79 mg. per cent with a rise to 155 mg. per cent at one hour and a fall back to 126 at three hours. A vitamin A tolerance test was normal. Skin tests were positive for milk and wheat. Following this admission the infant was continued on the milk-free diet, solids being added more cautiously than previously and she did extremely well. At the age of 2 years 3 months she weighed 28 pounds, appeared perfectly well physically, had no diarrhea, and was on a full diet minus egg and milk products.

Comment.—The correlation of this patients's symptoms with removal and addition of milk to and from the diet plus the negative findings for other

causes of her diarrhea, including negative stool culture, indicates that this is a case of milk allergy. It is also obvious from the history that there is intolerance to certain other foods, but from the study of the case it would appear that milk is the chief factor. The positive skin tests, while not proof of allergy, are confirmatory evidence.

CASE 8.—P. W., severe behavior problem.

This infant was first seen at the age of 4 months for a minor feeding problem characterized by slowness in feeding and some regurgitation. However, subsequent to this the milk formula was taken and tolerated well. The course was uneventful until 6 months of age, when the infant suffered mild tonsillitis which responded readily to treatment. At 10 months of age there was a severe bout of acute tonsillitis and thereafter there were frequent bouts with otitis media. During this period it was noted that the infant was extremely irritable, crying and screaming most of the time both day and night, sleeping poorly, and not responding at all to affection from the mother. This was attributed to the recurrent bouts of tonsillitis and otitis media and to anxiety on the part of the mother. However, there were two facts which implied that all the irritability was not due to these. First of all the mother was a stable, unexcitable woman who did not seem unduly concerned over the infant. Second, and more important, it was noted that during the times of the baby's respiratory infections when she was running a fever and would be expected to be much more irritable, her behavior improved considerably; and it was observed that these periods of improvement all coincided with the time the infant was taken off all of her feedings and put on clear fluids. In addition it was observed that after these bouts, as soon as milk was added to the diet, the behavior problem became much more severe again. With this in mind, milk was removed completely from the diet at 11½ months of age and the behavior was much improved, the infant being happy and contented again in spite of the fact that the tonsils and adenoids were still present and the infections were still recurring. At 13½ months the tonsils and adenoids were removed. Milk was left out of the diet and the infant did well, gaining weight rapidly, and being very happy and contented. Milk was then added to the diet and the original symptoms of irritability which were severe in nature returned. At 2 years 9 months she was started on an oral hyposensitization program with milk. One month later she could tolerate 2 tablespoonfuls of pasteurized milk, twice daily, without symptoms. However, the milk was increased too rapidly and when it was up to one-half glassful per day she again became irritable and considerable perineal irritation developed. At 3 years one month, when she was last observed, she could tolerate one-fourth cup of pasteurized milk daily without symptoms.

Comment.—This case is one of severe behavior problem caused by milk allergy. Proof of the milk allergy is shown by the fact that the symptoms repeatedly recurred when milk was added to the diet but disappeared as soon as milk was removed from the diet. The possibility that chronic and repeated infections were responsible was ruled out by the fact that the symptoms cleared when the milk was removed from the diet long before tonsillectomy and adenoidectomy were done, even though these infections continued.

CASE 9.—D. C., vomiting, diarrhea, acute anaphylactic shock.

This infant who was breast fed received an evaporated milk supplement at 2 months of age and again at 6 months of age, each time with resulting vomiting, diarrhea, and mild shock. At 6½ months, when the same procedure was repeated, he suffered acute anaphylactic shock, with recovery.

Comment.—This patient suffered acute anaphylactic shock from evaporated cow's milk at 6½ months of age.

This case is reported in detail elsewhere.[2]

DISCUSSION

Although the observed incidence of milk allergy (0.3 per cent) is low, this in no way detracts from the importance of this syndrome. In each case reported, the correct diagnosis made the difference between an acutely ill child and a relatively well child and, in fact, in two cases was lifesaving. Moreover, while this series of 3,000 patients contains many cases with relatively rare conditions such as neuroblastoma, hepatoblastoma, and adrenogenital syndrome, it contains no cases of brain tumor, diabetes, Hodgkin's disease, cretinism, diphtheria, lead poisoning, syphilis, and such diseases which are considered so important that they make up a large part of pediatric teaching in our medical schools and in hospital rounds. Milk allergy is therefore as important to the practicing pediatrician as are these diseases and should be considered in the differential diagnosis of all the conditions attributed to milk allergy which have been listed above. Otherwise the correct diagnosis will almost certainly be missed.

The literature on the incidence of allergy to cow's milk is extremely confusing as a result of the wide variation in incidence reported. This variation is due partly to the criteria used for diagnosis, since this diagnosis is largely a clinical one and is therefore likely to be influenced by the enthusiasm or otherwise of the observer for allergy. More important, the estimate of incidence is influenced by the pediatric population under observation. In the practice of medicine it is impossible to have a completely unselected series. If one has a reputation as an allergist it is inevitable that one will have more allergy in his practice than the other pediatricians in the same center. The same applies to one having a reputation for the care of newborn infants, for the treatment of diarrhea, for the treatment of colic, etc. Therefore it is impossible for any one observer, regardless of how honest his appraisal is, to give the true incidence of allergy to cow's milk.

Bain[3] states that milk is the most common single offender in eczema in infancy and childhood, and Hill[4] that it is the most important factor in many cases of infantile eczema. Davidson[5] found that milk produced symptoms in 40 per cent of 100 children over 6 years of age with perennial allergic symptoms and in 55 per cent of twenty allergic children up to 4 years of age, and concludes that in allergic syndromes of perennial occurence there is a 40 per cent or better chance of milk allergy playing a leading role in producing the symptoms. Buffum[6] states that milk is probably the commonest food cause of wheezing in babies and that colic and vomiting in early infancy strongly suggest milk allergy. Rosenblum and Rosenblum[7] concluded that cow's milk was the most common offender in sixty infants with gastrointestinal symptoms and eosinophils in the stools. Rothman[8] feels that milk allergy is a common cause of allergic diarrhea. Wessel and associates[9] found allergy to be the chief cause of colic in 12 per cent of forty-eight infants who suffered from colic and a contributing cause in another 19 per cent, and this allergy was presumably usually to milk since these were small infants. Hill,[10] on the other hand, feels that gastrointestinal symptoms such as vomiting and diarrhea are only occa-

sionally caused by allergy. Clein[11] states that approximately 7 per cent of infants are allergic to cow's milk in some degree, Donnally[12] and MaGee[6] that cow's milk is a comparatively frequent offender, Martin[13] that allergy is an important cause of infantile colic. Chobot[14] believes that milk sensitivity is a common occurrence. Rowe[15] finds that cow's milk allergy occurs in 20 to 30 per cent of all food-sensitive individuals and that infantile colic is often due to milk allergy. Loveless,[16] by means of a questionnaire sent to physicians, largely specialists whose encounter with allergy would be maximal, found an incidence of milk allergy of 1.5 per cent among 245,000 patients, both adults and children, by clinical standards and of 2.3 per cent among 180,000 patients by skin tests. Vaughan and Black[17] reported a questionnaire sent out by the Bureau of Health and Public Instruction of the American Medical Association in which the following estimates of the incidence of milk sensitivity were made: In children, Cooke estimated an incidence of 0.3 to 0.4 per cent, Rackemann less than 0.1 per cent, Waldbott 3 to 5 per cent, and Rowe 2 to 7 per cent. Vaughan in the normal population of children and adults estimated 1 to 1.5 per cent and Alexander in a large gastrointestinal clinic serving adults and older children estimated 5 per cent.

Something should be said about the absence of any cases of infantile colic alone attributable to milk allergy in this series. Among the 3,000 cases, several hundred cases of colic have been observed, and cases due to milk allergy have been sought for constantly. In spite of this I have not seen one that I can definitely prove to be so caused unless associated with other symptoms. (See case reports.) Many which were suspected of being due to milk allergy have been observed but were never proved either because they cleared spontaneously before the criteria of diagnosis listed above could be fulfilled, or because the mothers, with the preconceived idea that cow's milk is the only food fit for babies, refused to allow their infants to be put on a milk substitute. On the other hand, during the same period I have observed many infants with major allergy in whom colic was present and disappeared when their allergy was treated, often with the withdrawal of milk. I have also found milk allergy to be the cause of colic in a few referred patients with extremely severe colic who had no other evidence of allergy.

These observations on the rarity of milk allergy as a cause of colic are at variance with a great many reports in the literature. Wessel and associates,[9] for example, found allergy, presumably milk allergy in many cases, to be the chief cause of colic in 12 per cent of forty-eight colicky infants who were carefully studied, and a contributing cause in another 19 per cent. Clein,[18] in a study of 206 infants allergic to milk, found 31 per cent with colic as one of the symptoms. However, he does not state how many of these had colic alone. Sixty per cent of the infants had two or more major symptoms; eczema accompanied by allergic pylorospasm or colic, or both, was the most frequent combination and some had diarrhea and vomiting with colic. Martin[13] finds there is a much higher incidence of colic in infants of aller-

gic families and the incidence is higher still if both parents suffer from major allergy. He believes that allergy is an important cause of infantile colic. Rowe[15] believes that infantile colic is often due to milk allergy. In Rosenblums'[7] series of sixty infants with gastrointestinal allergy twenty-seven had colic but only three had colic alone. Cow's milk was the most common offender in this series. Buffum[6] states that colic and vomiting in early infancy strongly suggest milk allergy. Glaser[6] also feels that the severer cases of colic are often of allergic origin and lists presumptive and specific evidence for attributing colic to allergy. Hill,[10] on the other hand, believes that gastrointestinal disturbances in infants are occasionally caused by allergy but not commonly.

SUMMARY AND CONCLUSIONS

Three thousand infants and children seen in a private pediatric practice have been studied from the point of view of milk allergy. These have been consecutive cases except that all those suffering from major allergies, cases referred by a physician as possibly allergic, and patients coming directly because the mother considered symptoms to be allergic have been excluded, because these three groups would show an undue proportion of allergy in a practice made up of general pediatrics and pediatric allergy. An incidence of 0.3 per cent of definite milk allergy was found. This incidence is great enough that the practicing pediatrician should consider milk allergy in the differential diagnosis not only of infants and children suffering from major allergy but also in those suffering from a wide variety of symptom complexes both gastrointestinal and otherwise.

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THROMBOCYTOPENIC PURPURA IN MEASLES

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WHILE some degree of cutaneous extravasation of blood frequently accompanies the eruption of uncomplicated measles, gross hemorrhagic phenomena occur very rarely. The appearance of bleeding of severe degree in the skin or other organs during the course of rubeola produces the syndrome which has often been referred to as "black measles." That this is a rare complication of this common exanthematous disorder of childhood is attested by the fact that up to the present only twenty-five cases have been recorded in the world's literature. In sixty-three instances of thrombocytopenic purpura secondary to various infections studied by Heinld and Lindgren,[9] only one followed an attack of rubeola. The purpose of this paper is to add two proved cases of platelet deficiency with gross bleeding complicating measles to those already reported, to emphasize the serious character of this complication and the urgency for prompt recognition, and to record the effectiveness of steroid therapy in this disorder.

The first case of measles with severe hemorrhagic manifestations was reported by Jackson[10] in 1890 although others had probably been included prior to this time in discussions of purpura fulminans in which no consideration was given to specific etiology. Jackson's patient was a 5-year-old boy who developed extensive cutaneous bleeding following uncomplicated rubeola and died after three days of hemorrhage from the nose, mouth, urinary tract, and bowel. In 1896 Pucci[22] described a 7-year-old boy who bled into the skin and from the nose, mouth, bowel, and urinary tract late in the course of rubeola complicated by parotitis. Pain in the extremities, severe anemia, and splenomegaly were also present and death occurred two days following the onset of the hemorrhagic phenomena.

Since the reports of these two cases of measles with fatal hemorrhage, twenty-three others have been described in which bleeding phenomena have been noted. Of these, the relationship of rubeola to the hemorrhagic phenomenon is questionable in five. In one,[12] the measles was complicated by bronchopneumonia for which horse serum was administered. In another,[2] otitis media and probable glomerulonephritis were present. In a third patient the bleeding may have been related to the presence of bronchopneumonia or the use of sulfapyridine.[15] In one,[4] bleeding followed exposure to a known case of measles without the appearance of a characteristic measles rash. In one,[13] the platelet count was normal and twenty-two days elapsed between the onset of measles and the start of hemorrhagic manifestations.

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In ten cases of measles complicated by hemorrhage[1, 3, 6, 8, 11, 17, 18, 20, 24] there appears to have been no other cause for the bleeding tendency than the viral infection. In all of these patients bleeding occurred in the skin as well as other areas within fourteen days of the onset of rubeola. All showed a decrease in the number of circulating platelets and all survived. In four other instances,[14, 23, 25] the clinical pictures were similar to those in the ten just described, but no information is available concerning the number of platelets in the circulating blood. In three other cases,[7, 16, 19] rather extensive hemorrhage occurred; two survived and the other died. Neurological manifestations including coma, convulsions, and other signs of "cerebral irritation" in the presence of normal spinal fluid were observed in one patient by Nicholson.[19]

CASE REPORTS

CASE 1.—The patient was a 6-year-old white girl who, following typical prodromal manifestations, developed the characteristic rash of measles with moderate fever seven days prior to admission. The course of her disease was at first uneventful. The rash was fading and temperature was normal three days before admission. The following day bilateral earache and a hemorrhagic discharge from the right ear appeared. The next morning blood was present in both ears; 1 Gm. of sulfathiazole followed by two additional doses of 0.5 Gm. each was given during the day. In the evening, painless, gross hematuria was noted; this was still present at the time of entry to the hospital. There was no previous history of bleeding tendency in the patient or her family.

On admission to the hospital the patient's temperature was 103.4° F., pulse 130, respiration 28, and blood pressure 110/80. She was somewhat irritable but seemed in no acute distress. Her skin showed a fading measles rash, scattered petechiae, and a few areas of purpura. There were tenderness over both mastoids, fresh blood in both auditory canals, bilateral bulbar conjunctival hemorrhages, and petechiae which covered the mucous membranes of the mouth. The lips and nostrils were caked with clotted blood. The lungs were clear; the heart was of normal size with regular rhythm and no murmurs. The abdomen was not remarkable. The spleen was not palpated. There was no evidence of rectal bleeding. Blood was present at the vaginal orifice. Neurological examination was not remarkable.

The urine was grossly bloody; there was 1 plus albumin and an uncentrifuged specimen contained innumerable red blood cells and rare white blood cells. The white blood count was 24,700 with 83 per cent neutrophils, 51 per cent lymphocytes, 7 per cent monocytes, and 5 per cent metamyelocytes. The hemoglobin was 10.8 grams, and the reticulocyte count 2.4 per cent. Prothrombin time was 85 per cent of normal and bleeding time was 45 minutes. Tourniquet test yielded 15 to 25 petechiae per square inch with several small purpuric areas. The platelet count was 80,000 per cubic millimeter. There was no clot retraction in twenty-four hours. The patient's blood was group A, Rh negative.

Treatment included multiple blood transfusions, intravenous infusions of saline, sulfamerazine (1.0 Gm. followed by 0.5 Gm. every eight hours), liquid nourishment, and chloral hydrate for restlessness.

There seemed to be some improvement in the first twenty-four hours of hospitalization. The temperature dropped to 99° to 100° F., nasal and aural bleeding ceased, and no new skin lesions were noted. Hematuria continued, however, and the hemoglobin fell to 9.5 grams despite transfusion with about 500 c.c. of whole blood. The white blood count remained elevated.

Clinical improvement seemed to be maintained over the next two days, during which time she received 800 ml. of fresh blood. Sulfamerazine was discontinued on the second day. There was only slight, intermittent oozing of blood from the nose and lips, but hematuria continued, and temperature remained between 100 and 102° F. The platelet count rose gradually to 70,000 per cubic millimeter, and the white count dropped to 14,000 to 18,000. The quantity of hemoglobin on the fifth hospital day was 6.25 grams; 800 ml. of blood was administered on that day.

On the sixth day diffuse abdominal tenderness appeared and twenty-four hours later new areas of purpura and hematoma were observed. There was renewed hemorrhage from the ears and rectal bleeding was noted for the first time. These two days 1,450 ml. of blood was administered. On the eighth hospital day there was active bleeding from the ears, nose, mouth, and urinary, gastrointestinal, and vaginal tracts. The temperature rose to 103° to 105° F.. and the pulse rate to 120 to 150. The white blood count was 36,000, the hemoglobin 5.15 grams per 100 ml., the hematocrit 15.8 per cent, and there were 1.7 million red blood cells per cubic millimeter. The platelet count was 56,000. During this day and over the next eighteen hours 3,350 ml. of blood was given. Therapy with benzyl penicillin G, 40,000 units intravenously every two hours, was initiated.

During the following day bleeding continued in all areas, and the clinical condition deteriorated rapidly. Blood pressure was fairly well maintained, but respirations were shallow, with coughing on the slightest exertion, in spite of the administration of oxygen. By early afternoon, the pulse was 150 and respiration 60 per minute and fluttering. The patient gradually became stuporous and cyanotic and died in the afternoon of the ninth hospital day.

Autopsy Findings.—The peritoneal cavity contained about 300 ml. and each pleural space about 150 ml. of blood. The pericardium was normal and no hemorrhage was found in the pericardial sac. The epicardium was studded with many petechiae and the myocardium contained numerous hemorrhages of varying size. There were several petechiae in the endocardium, but it was otherwise normal. Both lungs were moist and bloody throughout. The spleen and liver were not remarkable on gross examination, save for pallor. There was marked hemorrhage in the perirenal tissues and petechiae were present on the surface of the kidneys. Both ureters were filled with blood. The adrenals were not grossly remarkable. The bladder contained bloody urine and there were hemorrhages in the wall. There were numerous petechiae in the mucosa of the stomach and small intestine in which a moderate amount of altered blood was present. About 20 ml. of fluid blood was found in the subdural space and a moderate amount in the subarachnoid space. There was a small area of hemorrhage in the left parietal cortex, but the remainder of the brain was not grossly remarkable. Cultures at autopsy revealed sterile heart blood and no growth from cultures of the lungs and left ear. Culture of the right ear revealed nonhemolytic *Staphylococcus aureus.*

Case 2.—A 4-year-old white girl had been exposed to a sibling who had had measles two weeks before. She developed typical prodromal manifestations followed by a characteristic rash one week prior to admission to the hospital. Fever and occasional vomiting persisted for three or four days and then subsided. On the day of hospitalization, slight epistaxis, hematuria, and the appearance of hemorrhage in the rash were noted.

There was no history of any bleeding tendency in the patient or her family. Birth and development were normal. The only prior illness was chicken pox. No drugs had been taken except for aspirin which was administered during the febrile period of the measles.

On admission, the patient's temperature was 99° F. (rectally), respiration 24, pulse 110, and blood pressure 90/60. Almost the entire skin was covered with a generalized hemorrhagic, maculopapular rash and small petechiae. The conjunctivae were injected. The ears were normal. There was a small amount of dried blood in both nares. The buccal mucous membrane was studded with punctate hemorrhages. There was some bleeding about the gums, the pharynx was injected, and the tonsils enlarged. There was a mild degree of generalized lymphadenopathy. The lungs were clear to percussion and auscultation. The heart was not enlarged, the rhythm was regular, and no murmurs were heard. No hepatomegaly or splenomegaly was detectable. There was no evidence of rectal or vaginal bleeding. Neurological examination was within normal limits.

The urine was grossly bloody, had a specific gravity of 1.024, and contained 1 plus albumin, innumerable red blood cells and 1 to 2 white blood cells. The hemoglobin was 11 grams per 100 ml., and the hematocrit was 33 per cent. The white blood count was 19,000 with 37 per cent neutrophils, 61 per cent lymphocytes, and 2 per cent eosinophils. No platelets were seen in the stained blood smear. The platelet count was 21,000. Bleeding time was 35 minutes, clotting time 3.5 minutes. Coombs test was negative. The stool gave a positive guaiac test.

Shortly after admission, the patient was given 40 mg. of ACTH in an intravenous infusion which was continued for eight hours. She also was given 75 mg. of cortisone orally every six hours, and 3 Gm. of KCl per day. Several blood transfusions were given.

On the following day improvement in the clinical condition of the patient was apparent. The rash began to fade, and the temperature remained normal. Microscopic study of the urine revealed only 2 to 3 red blood cells per high power field. The hemoglobin was 11 grams. The white count decreased to 10,000. The number of platelets increased to 124,000, but the bleeding time was still longer than 30 minutes. On the third day the urine contained no erythrocytes, and the platelet count was 138,000. There was gradual improvement in bleeding time and platelet count over the next few days. Pain, redness, and induration developed at the site of a cut-down, and *Staph. aureus* was cultured from the wound. Treatment with penicillin and later erythromycin resulted in gradual improvement of the infection and decrease in the white blood count and temperature, which had become slightly elevated. Starting on the sixth hospital day, the dose of cortisone was gradually decreased, and the drug was discontinued on the thirteenth day. The platelet count was 176,000 at this time. The patient was discharged from the hospital on the twenty-fourth day, fully recovered. At this time the hemoglobin was 11 grams, white blood count 7,450, platelet count 236,000, bleeding time 4.5 minutes, and clot retraction 50 per cent in two hours.

DISCUSSION

Although twenty-five cases of measles in which hemorrhagic phenomena appeared have been reported, five of these, as pointed out, exhibit a questionable relationship between the exanthematous disease and the bleeding because in two the hemorrhage was of minimal degree (platelet count normal in one), while in the other three the responsible factors may have been an allergic reaction to drug or horse serum or the presence of acute glomerulonephritis. If these cases are subtracted and the two new ones described in the present paper included, there are twenty-two documented patients who developed hemorrhagic manifestations attributable to dysfunction of the coagulation mechanism, probably directly provoked by infection with

TABLE

MEASLES COMPLICATED BY

Clinical and

INVESTIGATOR	AGE (YR.)	SEX	NO. OF DAYS BETWEEN RASH AND ONSET OF BLEEDING	AREAS IN WHICH HEMORRHAGE OCCURRED	PLATELET COUNT AT HEIGHT OF DISEASE	TIME FOR PLATELETS TO RETURN TO NORMAL (DA.)
Pucci[22]	7	m	2	Skin, nose, mouth, bowel, G.U. tract	—	—
Jackson[10]	5	m	—	Skin, nose, G.U. and G.I. tracts	—	—
Little[16]	1	f	11	Skin, nose, mouth, ear, G.I. tract	—	—
Fortune[7]	5	f	4	Skin, nose, G.U. and G.I. tracts	—	—
Nicholson[19]	17	m	5	Skin	—	—
Nicholson[19]	15	m	2	Skin, G.I. tract	—	—
Perlman[20]	4	–	7	Skin, mouth, G.U. tract	90,000	30
Sarrouy[24]	½	m	8	Skin, nose, mouth, G.I. and G.U. tracts	8,800	20
Miller[17]	5	m	4	Skin, nose, mouth, G.U. tract	10,000	20
Keizer[11]	2	m	5	Skin	70,000	25
Mills[18]	6	m	10	Skin, nose, mouth	37,300	90
Fisher[6]	3	f	8	Skin, mouth	14,500	50
Fisher[6]	6	f	6	Skin, mouth, eyes G.U. tract	11,000	30
Corbia[3]	9	f	2	Skin, mouth, nose, G.I. and G.U. tracts	5,000	30
Hansen[8]	8	f	14	Skin, nose, mouth, G.U. tract	80,000	21
Atta[1]	9	f	10	Skin, nose, mouth, G.I., G.U. tracts	15,000	40
Raisinghani[23]	4	f	6	Skin, nose, mouth, G.U., G.I. tracts	—	—
Wirth[25]	3	m	—	Skin, nose,	—	—
Wirth[25]	11	m	—	Skin	—	—
Lindsay[14]	2	f	3	Skin	—	—
Hudson	6	f	5	Skin, ears, eyes, mouth, bowel, vagina, urine	8,000	—
Hudson	4	f	4	Skin, nose, mouth, G.I. and G.U. tracts	21,000	14

I

HEMORRHAGIC PHENOMENA (22 CASES)

Laboratory Features

WHITE BLOOD COUNT × 1,000	ENLARGED SPLEEN	FEVER	COMPLICATIONS	THERAPY BEFORE BLEEDING	DEATH	DURATION OF BLEEDING (DA.)
—	+	+	Supp. parotitis	0	Yes	2
—	–	–	0	0	Yes	3
—	0	+	Pneumonia	0	Yes	8
—	+	0	0	0	No	7
—	–	–	? Encephalitis	0	No	Several
—	–	–	0	0	Yes	8
4.7	–	0	0	0	No	10
19.8	–	+	0	0	No	11
7.6	0	0	0	0	No	73
—	–	+	Pneumonia	0	No	19
—	0	+	0	Gamma glob.	No	14
23	0	–	0	0	No	10
4	0	+	0	0	No	6
6.5	+	–	0	0	No	3
—	–	–	0	0	No	>14
5.9	–	–	0	0	No	15
—	–	+	0	0	No	12
—	–	–	–	–	No	—
—	–	–	–	–	No	—
—	–	+	0	0	No	4
24	0	+	0	0	Yes	11
19	+	0	0	0	No	3

the virus of measles. All of the relevant data concerning these cases are presented in Table I.

An analysis of the data presented in Table I reveals a number of factors which characterize measles in which appreciable bleeding occurs. The average age of the patient is 6 years, with limits of 3 months to 17 years; in fatal cases, the average is 7 years. The death rate is 22.7 per cent. No sex differences are apparent. In one youngster, gamma globulin was given ten days prior to the onset of bleeding. Although three patients had complicating bacterial infections and one developed possible encephalitis prior to the onset of bleeding, no causal relationship between these and the hemorrhagic phenomena is apparent. The time of appearance of hemorrhage is recorded in only nineteen of the cases; the average interval between the onset of measles and the appearance of bleeding is about 6 days. Hemorrhage into the skin was present in all of the patients; other areas in which bleeding occurred were mouth, genitourinary tract, nose, gastrointestinal tract, ears, and eyes, in this order of frequency. The duration of bleeding is recorded in thirteen nonfatal instances and ranges from three to fourteen days, with an average of nine days. In the patients who died, the average duration of life from the time of onset of hemorrhagic manifestations is 6.4 days (range of 2 to 11 days). Of ten cases in which mention is made of splenomegaly, it was present in four. Fever was noted in ten of fourteen patients.

The white blood count shows considerable variation, the lowest being 4,000 and the highest 24,000. Studies of the number of circulating platelets are recorded in only twelve of the patients. In these, the thrombocyte counts ranged from 5,000 to 90,000, with an average of 30,900. The length of time required for the platelets to return to normal levels was about one month; this is exclusive of the case presented in this paper in which therapy with cortisone was employed.

On the basis of the features described in the literature, measles complicated by hemorrhagic phenomena has the following characteristic features: the disease appears at an age when rubeola is most common and its development is not related to the severity of the primary viral infection. Bleeding begins in from two to fourteen days after the onset of measles and continues for the same period of time if death does not occur. The skin is always involved, but hemorrhage may occur at any site, being most frequent in the mouth, gastrointestinal and genitourinary tracts, and nose. Fever is often present. The white blood count may be low, normal, or elevated. The level of hemoglobin is related to the extent and duration of bleeding. The platelet count is low and bleeding time and clot retraction are abnormal; the number of thrombocytes returns to normal in about one month in the patients who survive. The factors which may influence the outcome are primarily the intensity and duration of bleeding, the development of hemorrhage in vital areas, such as the brain or heart, the appearance of secondary infection, and the efficacy of any therapeutic measures which may be applied.

The reasons for the development of gross and potentially fatal hemorrhage in measles are unknown. That small amounts of extravasated blood are present commonly in the individual

lesions of the rash is well known and has little significance. This phenomenon may be related to changes in capillary fragility and the clotting mechanism. Perlman[20] has reported a consistent decrease in circulating platelets during the pre-eruptive and eruptive phase of uncomplicated rubeola. Other investigators[5, 21] have demonstrated an increase in capillary fragility in measles and one[5] noted a slight decrease in prothrombin at the time of appearance of the rash. Latent vitamin C deficiency which becomes clinically apparent under the stress of infection was suggested by Wirth[25] as the cause of the extravasation of blood into the eruption in uncomplicated measles. It is probable that all of these factors play a role in determining the character of the rash. The mechanisms by which marked decrease in the number of circulating platelets with the development of severe bleeding is brought about is at present unknown.

The prompt response of one of the patients reported in this paper to steroid therapy suggests that in this syndrome, as in certain others characterized by marked platelet deficiency, adrenal cortical hormones may be of considerable value in rapidly altering the course of the disease and in preventing death. The potential danger of the administration of cortisone in the presence of active virus infection was seriously considered before therapy was initiated. Because of the severity of the bleeding, however, it was decided that the risk of death from hemorrhage was greater than that of extension of the measles. So far as the writers can ascertain, this is the first reported instance of the use of steroids in this type of hemorrhagic disorder.

CONCLUSIONS

1. Extensive hemorrhage from various sites is a rare complication of measles; there are twenty-two cases of this syndrome (including the two new ones reported in this paper) which have been documented.

2. Two cases of severe thrombopenia with extensive bleeding complicating rubeola are reported; one patient died, the other survived.

3. Cortisone and ACTH may be of value in curing the hemorrhagic disorder and preventing death when extensive bleeding follows measles.

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UNILATERAL RENAL HYPERTENSION IN A GIRL CURED BY NEPHRECTOMY

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HYPERTENSION is uncommon in children. The causes in children, as in adults, may be classified as renal, cerebral or neurogenic, endocrine, cardiovascular, and essential. Many cases of hypertension occurring in childhood are due to renal causes. In addition to hypertension in bilateral renal diseases, unilateral renal hypertension occurs. The experimental work of Goldblatt and co-workers[1] aroused great interest in this type of hypertension. In children, a few recent clinical reports indicate a possibility of recovery from hypertension following an early nephrectomy. According to Glasser and Grossman,[2] there were only ten childhood cases reported in the literature where the blood pressure had remained at a normal level for at least one year after the operation, as compared with twenty-two cured cases in adults. It is stated that the cases of hypertension which may be cured by nephrectomy are comparatively rare. Cure by nephrectomy depends on an early diagnosis. In Japan no case of unilateral renal hypertension in childhood has been reported, as against six cases[3] in adults. We think that it is due to the fact that urological examinations frequently are not made in cases of hypertension in Japan.

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CASE REPORT

S. M., a 14-year-old girl had been in good general health. She had measles when 8 years of age. There was no family history of hypertension, brain diseases, or alcoholism. She was first seen at the time of admission on Dec. 11, 1952, with a complaint of nausea, vomiting, and headache. For three months previously, she had complained of a heavy feeling in the head, and sometimes of a dull epigastric pain. Eleven days before admission to the hospital she complained of headache, and early the next morning, had a convulsive attack followed by unconsciousness which lasted about two hours. Following this she complained of severe headache, nausea, and vomiting, and could hardly eat and sleep. The night before admission she had nasal bleeding.

She was somewhat emaciated. Temperature was 36.7° C. The pulse was regular and large with a rate of 80, and the respiratory rate was 20 per minute. Her mind was clear, but her expression one of exhaustion. The skin was pale and dry, and there was no petechia, edema, or abnormal pigmentation present. Dermographism was markedly positive. The conjunctiva was remarkably congested, but eyesight was normal. Foetor ex ore was intense and tongue was severely coated. The senses of taste and smell were normal as were phonation and swallowing. No abnormalities were observed on examination of the lung. The heart was enlarged to the left on physical and roentgenographic examinations. Cardiac sounds were pure, loud and forceful, with the second pul-

monic sound accentuated. The abdomen was soft and the liver and spleen were not palpable. Patellar and achilles tendon reflexes were increased. There were no abnormal reflexes, motor and sensory disturbances. The symptoms of pubertas praecox were not observed. Blood pressure was 162 mm./Hg systolic and 110 diastolic.

Ophthalmoscopic examination (Dr. K. Suga) was as follows: The eyes were normally prominent. The pupils equal, symmetrical, and reacted equally and accommodated to light. Eyesight was normal. Both papillas were congested and edematous, especially on the left side and the retina around both papillas was edematous. Several petechiae were seen on the fundus, and the retinal vessels were dilated and hypertrophied. Diagnosis: Papillitis o. utr.

Laboratory tests: Tuberculin reaction was negative. Urine, clear; specific gravity, 1.015 to 1.020; daily quantity, 400 to 900 c.c.; a trace of protein; urobilinogen positive; sugar negative. Microscopically the urine contained a few red and white blood cells, epithelium, and occasionally hyaline casts. Urine culture was sterile.

The findings of the electrocardiogram were those of oblique position of the heart.

Segmentation rate (Westergren) 65.

Nonprotein nitrogen was 1.15 Gm. per liter. Protein in serum was 8.95 per cent. Blood sugar was 1.29 Gm. per liter.

Occult blood in stool was negative. Stool: eggs of *Trichocephalus diasper* positive, otherwise negative.

The blood cell count showed 4,770,000 erythrocytes, hemoglobin 90 per cent (Sahli), and leukocytes 5,900 with 69 per cent polymorphonuclear cells, 20 lymphocytes, 11 monocytes, and 0 eosinophil and basophil.

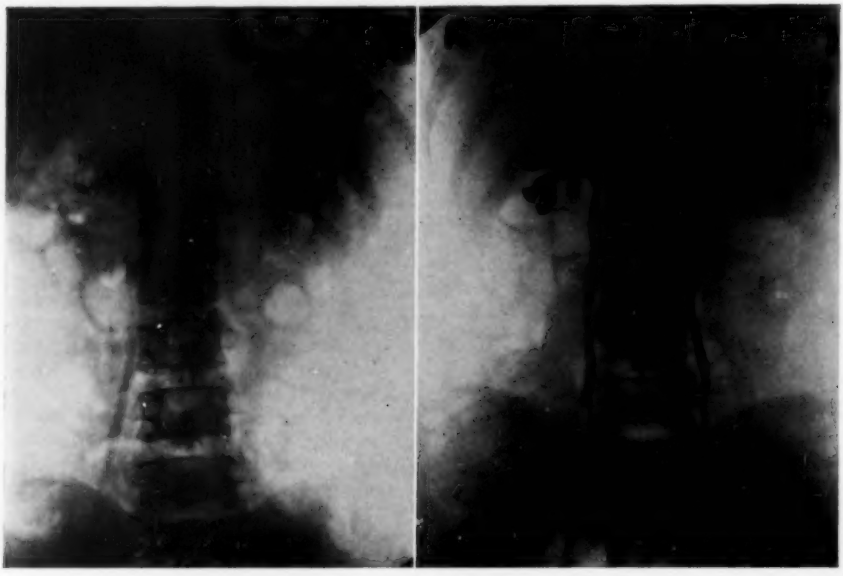

Fig. 1. Fig. 2.

Fig. 1.—Intravenous pyelogram showing normal right kidney. On the left, the renal shadow cannot be visualized.

Fig. 2.—Retrograde pyelogram. On the left, there is defect of shadow at the ureteropelvic juncture. Both pelves are normal.

A spinal puncture was performed on the day of admission. Initial pressure was 280 mm. H_2O and end pressure 130 mm. H_2O. The quantity of fluid removed was about 7 c.c. The fluid was water-clear; globulin reaction, negative; lymphocytes, 2; sugar content, normal. Culture and smear were negative.

Wassermann and Murata reactions as well as Takata reaction were negative both in blood and in cerebrospinal fluid.

Van den Bergh's reaction was negative.

Pneumoencephalogram showed nothing significant.

After admission, she developed occasional epistaxis and attacks of nausea, vomiting, and headaches. Symptomatic therapy was given. On the twenty-sixth day after admission, she again had several generalized convulsions of several minutes' duration, and the blood pressure rose to 197 systolic and 137 diastolic. She complained of pain on the deep parts of the eyes and had severe hyperemia of the conjunctivas. No changes were observed in eye grounds. Lumbar puncture showed elevated cerebrospinal fluid pressure with a normal protein level. There was no pleocytosis. Repeated punctures were unsuccessful in lowering the cerebrospinal fluid pressure.

Blood pressure rose gradually from 162/100 to 203/135.

On the forty-seventh day after admission, an intravenous pyelogram was performed, and Dr. N. Yano reported as follows: intravenous pyelogram (Fig. 1) showed good filling of the right renal pelvis with dye, but no dye was secreted on the left side. A retrograde pyelogram was performed with the following findings: cystoscopic examination of the bladder was normal; urine from the left kidney contained a trace of protein and a few erythrocytes, leukocytes, and epithelium. Indigo carmine, intravenously administered, appeared in good concentration from the right kidney in 2.5 minutes, but little dye was seen coming from the left ureteral orifice in 4 minutes and it did not become concentrated after 10 minutes. The site and forms of both pelvis were normal. A phenolphthalein test was performed, and its secretion showed 50 per cent of dye secreted in 30 minutes, with a total output of 75 per cent in 120 minutes. Culture of the urine secreted from the left ureter was sterile.

On the one hundred and fourth day after admission (March 31, 1953), a left nephrectomy was performed. The fluctuation in the blood pressure during and after the operation is shown in Tables I and II.

TABLE I. BLOOD PRESSURE DURING THE OPERATION

TIME AFTER OPERATION	SYSTOLIC	DIASTOLIC
Before	192	131
20 min.	165	124
45 min.	148	118
75 min.*	215	138
83 min.	185	132
100 min. (finished)	168	121

*Constriction of the main renal artery.

TABLE II. BLOOD PRESSURE AFTER THE OPERATION

TIME AFTER OPERATION	SYSTOLIC	DIASTOLIC
1 hr.	178	121
24 hr.	172	102
3 da.	135	88
15 da.	126	78
1.5 mo.	120	72
6 mo.	115	78
1 yr.	112	52
2 yr.	119	73

The pathological report of the left kidney and ureter (Dr. H. Hayashi) was as follows. The kidney, with a ureter of 10 cm. in length, weighed 110 grams and measured 4.5 by 6.5 by 11.0 cm. in diameter. Blood vessels at the ureter were slightly winding and dilatated. The pelvis was normal. The capsule stripped easily. The cortical surface was macroscopically normal. The pathological findings were: In occasional areas the glomeruli showed moderate swelling, and in areas, light hyalinization in the wall of the capsules. Lymphocytic infiltration was marked around the glomeruli and the

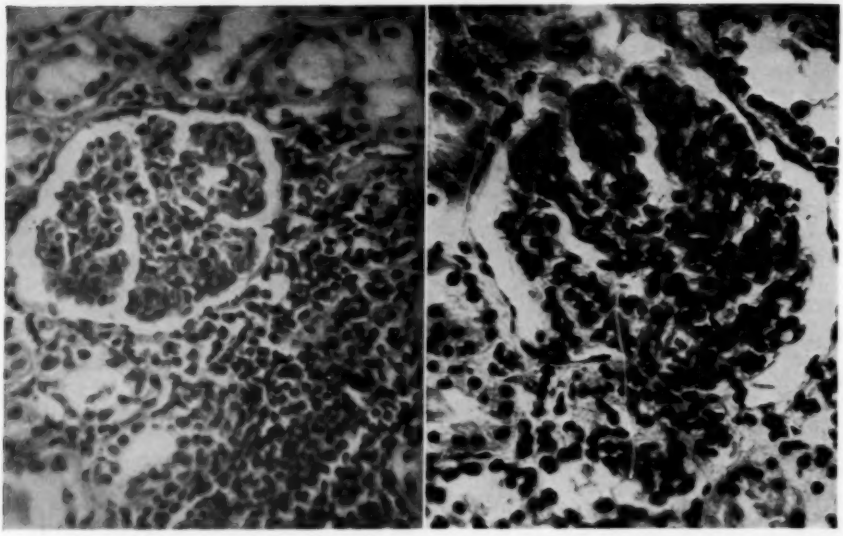

Fig. 3. Fig. 4.

Fig. 3.—Normal glomerulus and lymphocytic infiltration around the glomerulus in one area.
Fig. 4.—Adhesions between the glomerular tufts and their capsules in the other areas.

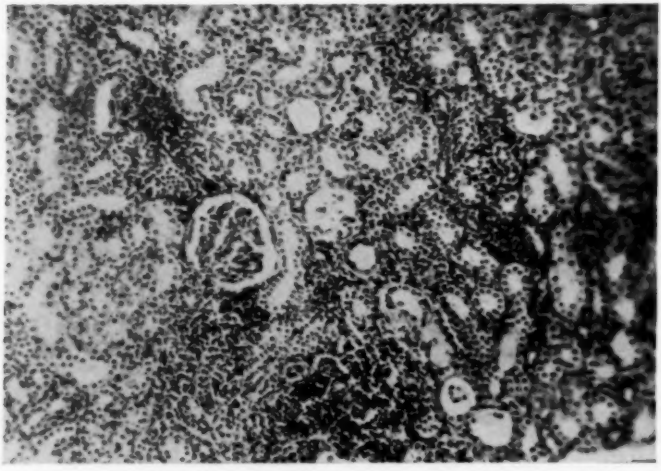

Fig. 5.—Lymphocytic infiltration in interstitial tissues and acute degenerative changes in the tubules.

glomeruli showed fibrotic changes and a tendency to hyalinization. Within the capsular spaces in some areas, a few erythrocytes and albuminous precipitate were found, and there were adhesions between the glomerular tufts and the capsules in other areas. The tubules showed moderately acute degenerative changes, especially marked at the main part, and were dilated irregularly in some areas. A hyaline substance within the lumens of the convoluted tubules was present.[1] Some of the tubular epithelium showed advanced degenerative changes and cloudy swelling. In occasional areas, the interstitial tissues were densely infiltrated with lymphocytes and mononuclear cells, and proliferation of the connective tissues was noted which extended to the subpelvic tissues. Lymphocytic infiltrations were noted around the venules. The arterioles were moderately thickened, and in some areas hyaline deposits were found in the walls of the arterioles. No findings of necrotizing arteriolitis and arteriolar nephrosclerosis were present in any area. Diagnosis: Chronic pyelonephritis.

After the nephrectomy, the urine became normal, the daily quantity increasing to 1,000 c.c. The subjective complaints disappeared gradually in about two weeks after the operation. The discs and the retinal vessels became normal and the retina around the disc became grayish turbid.

The patient was discharged on April 28, 1953. For two years following the operation the blood pressure remained at 118 systolic and 78 diastolic. Besides her clinical improvement and reduction in protein content of the urine, the most striking result has been found in the diastolic blood pressure. Her latest blood pressure reading was 110/72. After nephrectomy, although the improvement in the conjunctiva and eyesight has been striking, a definite residuum in the eye grounds remained.

DISCUSSION

In children, essential hypertension is uncommon and the majority of the cases of hypertension are associated with renal disease. Campbell[4] reported that the hypertension due to unilateral renal disease in children has been observed in about 1 per cent of patients with hypertensive vascular disturbance subjected to a complete urologic study. Since the original publication of Butler,[5] there are many reports in the literature on unilateral renal processes causing hypertension.

According to Schlesinger and McCarthy, there are three kinds of kidney disease to be considered: (a) congenital hypoplasia or aplasia, (b) chronic pyelonephritis, which is often found in combination with (a), and (c) congenital anomalies of the main renal artery, which leads to ischemia of the diseased kidney. As reported in the literatures,[6-12] the causes of unilateral renal hypertension are as follows: pyelonephritis, hydronephrosis, renal tuberculosis and tumors, cystic kidney, nephrolithiasis, hypoplasia and aplasia, obstruction to the renal circulation, renal embolism, perirenal hematoma, nephroptosis, urethral obstruction, etc. In children, acute poliomyelitis and the adenogenital syndrome were reported as additional causes.

The experimental studies of Goldblatt and co-workers explained the relation between hypertension and certain types of unilateral renal diseases. By the constriction of one renal artery, producing renal ischemia, a rise of blood pressure had been seen and the removal of the constricted kidney resulted in a prompt return of the blood pressure to normotensive levels. Although these experimental works still have an uncertain sphere on unilateral renal hypertension, and the percentage of cures following nephrec-

tomy reported in the literatures is low, it is thought that the removal of a unilateral diseased kidney producing hypertension is perhaps the best method for treatment. As irreversible pathologic changes in the remaining kidney may be present, early nephrectomy should be performed. In our case the arteriosclerotic changes in the diseased kidney were not found, so it was considered no irreversible changes were present. We consider the unilateral pyelonephritis a cause of the hypertension, and we consider the successful outcome due to the nephrectomy. However, a study of the literature reveals only a few patients cured or benefited by nephrectomy for unilateral renal diseases. Cure should not be assumed unless the diastolic pressure in particular remains within normal limits for at least two years. Generally speaking, the younger the patient and the shorter the duration of the hypertension, the better the result.

SUMMARY

A girl, 14 years of age, with extreme hypertension, complained of headache, vomiting, and convulsion for three months. As the form and site of the kidney on retrograde pyelogram was almost normal, the diagnosis could not be determined for three months. Following a unilateral nephrectomy of the left pyelonephritis, she became free from symptoms for two years. She has been able to attend school, and has grown normally with no symptoms or signs of cardiac or renal disease. Only on the eye grounds a linear gray-colored turbidity around both discs persisted.

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TEMPORARY ADRENAL INSUFFICIENCY WITH ASSOCIATED PYLORIC STENOSIS

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THE purpose of this report is to record a case in which two conditions with similar symptoms are represented.

In recent years many case reports have been published dealing with disturbances in the secretions of the adrenal cortex. The functions about which we have a better established knowledge are: (1) The regulation of the sodium, potassium, and water balances, which is controlled by the hormone 11-desoxycorticosterone. (2) Sugar metabolism, controlled by the hormones related to 11-dehydro 17-hydrocorticosterone. This group of steroids has been designated the "S" hormone. (3) Anabolic and nitrogen retention, controlled by the group of steroids related to the androgens. These have been designated as the "N"hormones because of their effect on nitrogen balance. Each of the hormones can be independently variable with an increase or decrease of one or the other in many combinations. A classification of adrenal insufficiency in infancy based on reported cases has been formulated by Gappert and associates.[1] These conditions are also discussed by Wilkins.[2]

Most of the reported cases are concerned with a permanent deficiency of the adrenal cortex hormone. It is with the temporary hypofunction of the adrenal gland which occurs in early infancy during the transition from the "fetal" to adult reticular zone that we are concerned in this paper. Clinical evidence of this situation was presented by Jaudon[3, 4] in 1946 and 1948.

The question of whether an actual deficiency in adrenal cortical function does exist in these cases is difficult to answer due to lack of histological material. It is partially answered in the affirmative by the clinical and laboratory response to replacement therapy.

Another interesting feature, at least as pertaining to this case and one other reported by Morec,[5] is whether there is any causal relationship between adrenal cortical insufficiency and pyloric stenosis. It is doubtful in the case to be reported if the cortical insufficiency was due to the increased stress caused by a pyloric obstruction. Since vomiting was present soon after birth it is more likely that adrenal insufficiency was the cause, as vomiting due to pyloric stenosis is not characteristically present until after the second week of age. Another thought for speculation is whether the vomiting would have ceased, and if surgery could have been avoided if replacement therapy was instituted at the start.

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CASE REPORT

T. R., a 6-week-old white female infant, was admitted to the hospital on Oct. 1, 1954, because of vomiting. The family history, including the patient's four siblings, was entirely negative. Birth weight was 2.4 kilograms. Vomiting was noted to have occurred after the baby received her first feeding at 12 hours of age. Following this the baby continued to vomit various amounts of almost every feeding while in the hospital nursery. After discharge, the mother made various changes in the formula with some improvement. However, the vomiting persisted and increased in both amount and frequency. The vomiting was described as forceful in the latter stages and never contained any green material. The stools were described as infrequent and scanty in amount. It was noted that although the baby would feed hungrily at the beginning of the feeding, she would become fatigued after taking 30 c.c. The baby was described as being active despite her severe state of undernutrition.

Examination on admission revealed a severely dehydrated and marasmatic infant. There was generalized absence of almost all subcutaneous fat. The skin was of a grayish hue. Despite the poor clinical appearance, the infant cried lustily and resisted examination vigorously. The only other clinical finding was a questionable pea-sized mass in the abdomen in the region of the pylorus. The diagnosis of pyloric stenosis was made.

A large pyloric tumor was found at surgery, and a Ramstedt operation was performed. Eight hours after, oral feedings of dextrose solution were offered and retained during the next twelve-hour period. However, vomiting recurred and despite parenteral fluids a steady weight loss ensued. Feedings were then given through a tube which was passed into the duodenum. Despite adequate amounts of high caloric formulas fed through the tube there was a continuous loss of weight. It should also be mentioned that from admission to this point the body temperature was subnormal, ranging between 78° and 79° C., rectally. At this stage the possibility of adrenal insufficiency was suspected.

Replacement therapy was instituted in the form of DOCA (desoxycorticosterone acetate), 2.5 mg. daily. One gram of salt was also given daily. Twelve hours after the hormone was started all vomiting ceased and the course was a rapid uphill one. Weight gain averaged 1 to 2 ounces daily. The baby began taking her feedings avidly. Her color returned to normal, body temperatures returned to normal, and for the first time since hospitalization she smiled and wanted to be fondled. The above-mentioned dosage of DOCA was administered for twelve days and then lowered to 1 mg. daily. In the twenty-four-hour period following this reduction in dosage there was no weight gain, and a loss of one ounce occurred in the next twenty-four-hour period. However, following this there was a return of a daily weight gain. After five more days the DOCA and salt were discontinued. The baby continued to do well and was discharged on the twenty-ninth day after therapy was started, with a weight gain of 19 ounces in that time.

The laboratory data are shown in Table I.

TABLE I

DATE	Na	Cl	K	CO_2	UREA N.
10/ 4/54	139	84.6	7.5	31.7	11 mg.
10/ 6/54		99.2			
10/20/54	146		6		4.9

In meq.

DISCUSSION

The question arises as to whether we are dealing with two separate entities, or if there is a specific relationship between the two. It has not been proved conclusively that hypertrophic pyloric stenosis does exist from birth, and it is felt by

some that the defect is not one of congenital origin. Some authors believe the hypertrophy of the circular muscle fibers of the pyloric sphincter to be a congenital anomaly with spasm of the muscles secondary, and others that the spasm is primary and the hypertrophy the result of the increased muscular activity. Of the latter group no definite etiology of the spasm is offered other than a functional disorder of the nerves of the stomach and pylorus, or a functional obstruction existing primarily, which produces a reflex irritation and stimulus to the nervous mechanism, causing spasm of the musculature. Thus it is open to speculation that there may be a direct relationship between insufficiency of the adrenal cortex and spasm of the pyloric musculature. Perhaps further investigations along this line might prove interesting.

SUMMARY

A case is presented with clinical evidence of both adrenal cortical insufficiency and hypertrophic pyloric stenosis. Pyloric stenosis was confirmed surgically and repaired with no improvement in the original symptoms. A marked and immediate response to desoxycorticosterone and salt therapy occurred.

[In addition to this case and the case reported by Morec, the Editor has knowledge of two other cases of pyloric stenosis associated with clinical evidence of adrenal insufficiency.]

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SEVERE RESPIRATORY DEPRESSION FOLLOWING NASAL INSTILLATION OF TETRAHYDROZOLINE HYDROCHLORIDE

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A NEW nasal decongestant, tetrahydrozoline hydrochloride* was introduced into therapy late in 1954 after extensive animal experimental studies and clinical trials. Soon after its introduction, a depressant effect upon the central nervous system was noted in a few individuals, particularly in children less than one year of age. Caution notices were then sent to practicing physicians by the manufacturer.[1]

The present report deals with an alarming reaction observed in an infant following the administration of tetrahydrozoline hydrochloride. To our knowledge there are no previous published reports of serious reactions caused by this drug.†

CASE REPORT

On Jan. 26, 1955, a 10-week-old boy (Flower-Fifth Avenue Hospitals, Case No. 13349, K. S. W.) was admitted to the service of one of us (W. L.) because of severe central nervous system depression, manifested by stupor and shallow breathing of fourteen hours' duration, culminating in apnea and cyanosis, four hours prior to admission. This episode occurred after the mother had administered tetrahydrozoline hydrochloride nasal solution.

The patient had been well until two days prior to admission when he was noted to have a "cold" with a nasal discharge but without fever. Despite the administration of oral penicillin and the use of phenylephrine hydrochloride* nose drops, one in each nostril every twelve hours, the nasal discharge persisted. The referring physician, therefore, prescribed tetrahydrozoline hydrochloride, 0.1 per cent in a plastic squeeze bottle. Sixteen hours prior to admission the mother instilled one drop of the drug into each nostril of the infant by inverting the squeeze bottle. Two hours later the child was observed to be unusually lethargic and to have stertorous respirations. Four hours after the instillation, the breathing was irregular and gasping in nature "much like hiccups," according to the mother. Two hours prior to admission the referring physician was called to see the child and found him flaccid, apneic, and severely cyanotic. As an emergency measure, with the aid of police facilities, he administered oxygen under positive pressure, Adrenalin, and cortisone. The baby was hospitalized soon afterward, when minimal improvement was noted.

The baby was a product of a full-term uncomplicated gestation and a normal spontaneous delivery, weighing 7 pounds 14 ounces at birth. Growth and development were normal, the weight on admission being 12 pounds 14 ounces. Two older siblings had questionable histories of inhalent allergies.

From the Departments of Pediatrics and Pharmacology, New York Medical College, Flower-Fifth Avenue Hospitals.

*Tyzine, 2-(1, 2, 3, 4-tetrahydro-1-naphthyl)-imidazoline-HCl, 0.1 per cent in aqueous solution, Pfizer Laboratories, Brooklyn 6, N. Y.

†See addendum.

*Neo-Synephrine.

Physical examination on admission revealed a well-developed, well-nourished pale baby appearing somnolent, and suffering from hiccups. The respirations were so shallow that the fact that he was breathing at all was ascertained with difficulty. He was afebrile, and had good skin turgor. The pulse was 140 per minute, and the anterior fontanel was open and under normal tension. The pupils were normal and equal in size, and reacted to light. Funduscopic examination revealed no papilledema or vascular abnormalities. There was nasal and retropharyngeal mucopurulent discharge. Slight nuchal rigidity was noted. Kernig and Brudzinski signs were negative. The chest was symmetrical and manifested normal resonance fremitus and auscultatory findings. The heart was not enlarged, its rhythm was regular, and no murmurs were heard. The abdomen was moderately distended and tympanitic. The blood pressure was unobtainable. There were no further demonstrable abnormalities.

Laboratory Findings.—A blood count showed the following values: hemoglobin 11.5 grams per 100 c.c., erythrocytes 4,000,000 per cubic millimeter, leukocytes 15,500 per cubic millimeter with a normal differential. The urinalysis revealed no abnormal findings. The blood culture was sterile. Spinal fluid was withdrawn under normal pressure and manifested seven white cells and normal chemical constituents. The spinal fluid culture was sterile. X-ray of the chest was not remarkable.

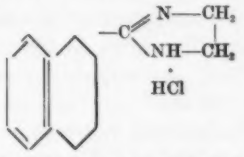
The child was kept in oxygen for the first twenty-four hours. His respirations gradually improved and he became more alert. On the second day, he ran a temperature elevation to 101° F. which lasted about twelve hours and fell by lysis.

Additional therapy included penicillin, streptomycin, and vitamin supplementation. The child was discharged, recovered, on the fourth hospital day.

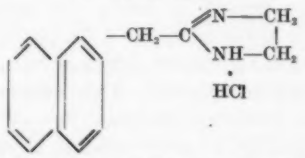
DISCUSSION

Central nervous system depression to the point of toxicity had been noted with other pressor-amines, especially alpha-napthal-2 methyl imidazoline,* to which the present drug is related in structure.

Although these two derivatives of imidazoline exhibit many of the pharmacological actions of epinephrine and its congeners, their structure departs greatly from that of the conventional



2-(1,2,3,4-tetrahydro-1-naphthyl)-imidazoline-HCl; **Tyzine**



2-(1-naphthylmethyl)-imidazoline-HCl; **Privine**

sympathomimetic amines. It is believed that these imidazolines act directly on adrenergic effector cells, but it is not known whether the receptor mechanism is the same as that for epinephrine. The outstanding pharmacological action of naphazoline, the better known of the two, is constriction of peripheral blood vessels. It does not share the ability of epinephrine to stimulate the myocardium or the central nervous system. On the contrary, it has been known for some time that naphazoline is capable of causing sedation in infants and young children. Although the amounts absorbed after topical application cause

*Privine; naphazoline.

little more than somnolence, severe degrees of depression have followed the accidental ingestion of few milliliters of naphazoline. This apparently applies in equal measure to the drug under discussion.[2-7]

Tetrahydrozoline hydrochloride has apparently also a purely local vasoconstrictive effect. It likewise possesses a definite depressant effect on the central nervous system demonstrated in animals[8] and men,[1] which has not as yet been adequately studied.

This depressant effect has occurred on supposedly routine dosage schedules in children, particularly those under one year of age.[1] In our case, and it must be presumed in others as well, it may have occurred because of idiosyncracy to the drug or possible overdosage caused by using the inverted plastic spray bottle as a dropper. Under such conditions dosage is certainly difficult to control. This effect may range from mild sedation to coma.[1] In our patient it progressed to a rather alarming stage of complete apnea and severe cyanosis.

Treatment consisted of oxygen under pressure until regular respiration was established. The child was then permitted to "sleep off" the sedative effects in an oxygen tent, with provision for adequate hydration. Animal studies show that the use of stimulants is contraindicated because it contributes to the aggravation of symptoms.[1]

The findings in our case point to tetrahydrozoline hydrochloride as the responsible agent for the following reasons: (1) the depressive reactions clearly followed the administration of the drug, developing within two hours after nasal instillation; (2) closely similar reactions to this drug and to the chemical congener, naphazoline, have been reported[1-6]; and (3) there is no other cause in this instance to which we feel that we can reasonably attribute this severe depressant reaction.

It is conceivable that with sufficient dilution of the drug for use in infants, these reactions could be obviated. A weaker solution (0.05 per cent) in a dropper bottle is available. Parents should be made aware of the inherent danger of unsupervised medication, especially in infants, and should be warned to discontinue the drug at the first sign of a depressant reaction. The not uncommon use of spray bottles for medication in infants should be discouraged.

SUMMARY

A case of severe respiratory depression following the nasal instillation of tetrahydrozoline hydrochloride nose drops in a 10-week-old boy is described. The pharmacology and toxicology of this drug and related compounds are briefly discussed. Caution is advised in the administration of this medication to infants.

We wish to thank Dr. Lawrence Slobody for his interest and helpful suggestions. The cooperation of the Medical Department of the Pfizer Company is greatly appreciated.

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ADDENDUM

Subsequent to the preparation of this report, there has appeared in the *Journal of the American Medical Association*, correspondence describing similar reactions to Tyzine in infants.*

*Greenstein, N. M., and Friedman, H. T.: Correspondence, J. A. M. A. 157: 1153, 1955.

"Spock"—Two Centuries Ago

If we could prevent the shrieking of children, it would be of great advantage, because much shrieking may have many dangerous consequences: for example, the blood is retained in the brain, for it can easily enter the *arteria pulmonalis*, but cannot well get out again; besides the child grows dry in the throat, feverish, and gets easily a rupture. The whole art of silencing a child consists, 1. In removing the cause of its shrieking; or 2. In amusing it with something which strikes its fancy, and wholly engates its attention, and makes it forget what it cried for.

The cradle or the bed of the children ought not to stand near any stove, fireplace, or near a wall, where a chimney passes by from any room below, in which a fire is kept: for thereby it would be used to such a warmth, that it would get catarrhs at the nose, on being afterwards carried to the window, or some other part of the room; the cradle ought also to be put in such a direction, that a strong light may not fall upon the child's eyes. A full grown person will find it offensive to his eyes by working on a table opposite to the window. It is not only necessary for the room to be kept clean, in order to prevent the child's getting the scab, but the nurse ought also to keep herself neat and clean: likewise the child's linnen, rags, flannels etc. should frequently be shifted.

Tickling children is very dangerous: they may from that get convulsions, and even lose their lives; . . .

From the English edition (1776) of the Swedish text *The Diseases of Children and Their Remedies* by Rosen von Rosenstein (1771).

BILATERAL RENAL AGENESIS AND OLIGOHYDRAMNIOS

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BILATERAL renal agenesis is relatively rare, as indicated by a review of the literature by Frumpkin and Marz[1] in 1954, who found only 166 reported cases to which they added four more. Of additional interest is the statement by Potter[2] that in all thirty of her cases there has been a report of a reduced amount of amniotic fluid, but no definite proof that its absence was not due to previous rupture of the membrane despite a negative history. She raises the question of the possible significance of this as an indication of the role the fetal kidney may play in the formation of amniotic fluid. She further states that none of the patients she has studied have survived more than eleven hours.

The patient presented is of special interest because this baby was born completely encased in the intact amniotic membranes in which there was no amniotic fluid and the infant survived for five days.

CASE REPORT

Newborn female M. (H. H. No. 101-882) was born on Aug. 8, 1954, at term with a birth weight of 5 pounds 3 ounces. Her mother was a 30-year-old Mexican woman who had had six previous pregnancies, all resulting in normal, living children. The last of these children had been a breach delivery, otherwise there was no unusual obstetrical history. There were no difficulties during the pregnancy with the present infant and she was delivered from the L. O. A. position. The labor lasted one hour twenty-seven minutes.

At birth the infant was at first thought to be a monster because it was contained within an intact amniotic sac. The sac was applied tightly to the infant and appeared to contain no fluid, and no opening could be found in it. The membranes were opened and the infant extracted. No amniotic fluid was present. The skin was found to be covered with a thin coating of gummy, white vernix. There was an immediate, faint cry followed by thirty seconds of apnea, after which the infant's respiration resumed. The respiratory efforts were poor, but the infant's color remained fairly good. The baby was placed in an incubator and given antibiotics prophylactically because of the respiratory distress.

On examination shortly after birth the baby's appearance was noted to be somewhat unusual. The neck was short with a low hairline posteriorly. The head was hunched forward and the shoulders were rounded. The head itself did not seem to be abnormal and the ears were normally placed. Crepitant râles were audible over all lung fields, and there was moderate costal retraction on inspiration. The remainder of the physical findings were normal. The external genitals appeared to be normal for a female infant. During the next three days there was little change. The baby nursed fairly well and the stools were normal. No abnormality of the urinary tract

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was suspected until the fourth day of life. Urination was recorded as occurring during the first three days of life. Since it was later determined that it was impossible for the baby to urinate, it is difficult to know whether these were completely false reports of urination or whether the high humidity in the incubator caused the diapers to be wet enough to mislead the person changing them. The humidity was kept high enough so that there were visible droplets of water on the walls and top of the incubator. In any event, the baby was doing poorly by the end of the third day and since there were no more reports of urination from that time on, urinary tract difficulty was suspected. The blood urea nitrogen was 60 mg. per cent on the fourth day of life. Attempts to pass a catheter into the urinary bladder were unsuccessful. A scout film was reported as showing a normal chest and abdomen.

After marked distention of the abdomen developed it was decided that an exploratory laparotomy was indicated. The operation was terminated when the kidneys and ureters were found to be absent. The baby died immediately postoperatively at the end of the fifth day of life. At autopsy a complete absence of the kidneys, ureters, uterus, ovaries, and Fallopian tubes was demonstrated. The cervix was present only as a small nubbin of tissue projecting into the vagina. The bladder was a cordlike structure extending cephalad along the anterior abdominal wall, and no external or vaginal opening of the urethra could be found. The adrenal glands were flattened and were applied closely to the posterior abdominal wall. The lungs were pink, crepitant, and floated in water. Their gross appearance was not abnormal. Microscopic sections of the lungs revealed only focal areas of hemorrhage and atelectasis.

DISCUSSION

This case is reported partly because it is of interest that a baby with bilateral renal agenesis lived five days. Of greater interest is the fact that this baby was born completely enveloped in an apparently intact amniotic sac which contained no amniotic fluid. The absence of amniotic fluid has been reported before in association with bilateral renal agenesis,[2] but in general there has been some lack of certainty as to possible prior rupture of membranes. We do not believe this is so in this case. Bates[3] has reported a patient with bilateral renal agenesis delivered by cesarean section in which the amniotic fluid was found to be entirely absent and there was no history of previous rupture of the membranes. However, Hinman[4] states that renal aplasia has occurred many times without abnormalities in the amniotic fluid, but he cites no specific cases.

There are considered to be several possible mechanisms of the formation of amniotic fluid: (1) fetal urine; (2) a transudate from maternal blood; (3) secretions through the amniotic epithelium; and (4) various combinations of the preceding mechanisms. Makepeace and associates[5] indicate that fetal urine may play a significant part in the formation of amniotic fluid late in pregnancy. However, studies by Vosburgh and co-workers[6] would suggest that the amount of amniotic fluid and the rate of exchange are so great as to make it questionable that the fetal urine could alone account for this relatively large volume of fluid.

This case would tend to further the concept that fetal urine does play some part in the formation of amniotic fluid or it would be necessary to assume an abnormality of the amniotic fluid formation in addition to the renal agenesis.

SUMMARY

A case of bilateral renal agenesis is reported in which oligohydramnios seems to be definitely established by the fact that the baby at birth was completely enveloped in the intact amniotic sac which contained no amniotic fluid. The baby survived five days.

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PTERYGIUM SYNDROME

ALEXANDER EMED, M.D.
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THE pterygium syndrome is a complex of congenital anomalies. There were 225 cases of this condition reported in the world medical literature up to 1952, and Rossi and Caflisch[1] reviewed 197 of these cases. Caffey[3] noted the paucity of references to this syndrome in the American literature. Although Turner,[2] in 1938, described patients with this condition, the so-called "Turner syndrome" represents but one particular form of this anomaly. The pterygium syndrome (Bonnevie-Ullrich syndrome) has a rather wider application. The term "ovarian agenesis" is also not all-embracing, since many male patients presenting characteristic features have been described.

The clinical picture is not uniform. The characteristic feature is a prominent fold of skin, usually bilateral, containing muscle, nerves, and blood vessels. In the majority of cases, this fold is seen in the neck, but may occur in other parts of the body, including the axilla, cubital fossa, popliteal fossa, and interdigital spaces. Such folds may be seen in a number of sites in the same patient, and there are symmetrical and asymmetrical forms. Other distinctive signs include lymphangiectatic edema of the limbs and hyperelasticity of the skin ("cutis laxata"). Various additional deformities may accompany the above principal features.

Among the classifications presented by various authors, that of Rossi and Caflisch[1] divides cases of the syndrome into five groups, based on sex, symmetry, Klippel-Feil deformity, muscle abnormalities, and limitation of joint movement. The theory of Bonnevie[4] on the pathogenesis of this condition through the physical action of blebs of liquor in the fetal nervous system has not been generally accepted.

CASE REPORT

B. C., female, born in this hospital, was seen at the age of 5 days. The mother appeared to be a mental defective of a mild degree. Two of her other six children had congenital heart disease and one other suffered from congenital pyloric stenosis, being cured by the Ramstedt operation. The father and the remaining three children were well. Details of other relatives were not available.

This pregnancy, the seventh, was not unusual. The delivery was spontaneous and without complications, but the infant was in a state of asphyxia, from which she recovered rapidly. The birth weight was 2,600 grams, the length 49 centimeters, and the head circumference 34 centimeters.

On examination, the infant was weak and poorly developed. She appeared unduly somnolent and the skin and lips showed moderate cyanosis. There was marked pallor, and the facies gave the impression of probable mental deficiency. The scalp showed a heavy

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growth of hair. The ears were deformed, prominent, and were set much lower than usual in relation to the skull. The bridge of the nose was broad and depressed. The neck was short and there was a prominent web of skin extending from the mastoid region to the acromioclavicular area. The palate was narrow, high, and arched. The skin of the forearms showed marked laxity with increased elasticity. The fingers were held in a

Fig. 1.—The patient, aged 5 days.

state of flexion with the exception of the distal and middle phalanges, which were in a position of extension. The fingers could be straightened with ease, but immediately returned to their former position. Both hands showed slight skin webbing of all the interdigital spaces, and the nails were underdeveloped, short, and thin. The heart rate was rapid, and a systolic murmur was heard over the area of the aortic valve. Physical examination of the lungs revealed no abnormal finding. The abdominal wall showed poor muscle tone, and the liver and spleen were not palpable. The skin of the upper inner thigh region showed increased laxity and elasticity, similar to that noted on the forearms. The elitoris was prominent and unusually well developed. Figs. 1 to 4 show the outstanding physical findings.

The x-ray examinations revealed the following: The heart showed generalized enlargement, and there were signs of bronchopneumonia at the base of the right lung. The distal end of the radius showed dislocation. The skull and spinal column showed no abnormality.

Fig. 2.—Deformity of ear and webbing of neck.

Dyspnea became severe on the seventh day of life, and death occurred within a few hours.

At autopsy, the important features were noted in the cardiovascular, respiratory, and genitourinary systems. The heart showed hypertrophy of the right ventricle, a patent foramen ovale, and a high interventricular septal defect. A large patent ductus arteriosus and coaretation of the aorta were present. The lungs showed bilateral bronchopneumonia with fibrinous pleurisy. The mesentery base was

Fig. 3.—Cutis laxata and deformity of fingers.

Fig. 4.—Hypertrophy of clitoris and cutis laxata.

short. There was a right double kidney and ureter. The neck of the uterus was hypertrophied, and the ovaries were thin and elongated.

COMMENT

Physical examination of this infant showed gross deformities of the head and neck, the skin of the forearms and the thighs, the fingers and the nails, and an organic systolic murmur. Autopsy confirmed the presence of severe congenital heart disease and the characteristic findings of underdeveloped ovaries and hypertrophy of the neck of the uterus. The family history of mental deficiency and congenital deformities is of interest. This particular patient corresponds to the "status Ullrich bilateralis" type in the classification of Rossi and Caflisch.

SUMMARY

A 5-day-old infant presenting the pterygium (Bonnevie-Ullrich) syndrome is described.

I am indebted to Drs. B. Ostrowski, B. Gelei, and S. T. Winter for their help.

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INTRAPERICARDIAL TERATOMA

With Report of One Case

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ALTHOUGH teratomas are frequent in children, and their occurrence is not rare in the mediastinum, an intrapericardial localization is not common. The literature available to us has yielded only eight cases.

REVIEW OF PREVIOUS CASES

Joel[1] reported a cystic teratoma in a child 14 years of age adherent to the adventitia of the pulmonary artery. Grimm[2] reported a 3-month-old baby with a teratoma that completely obliterated the outline of the heart. The tumor was located in the anterior portion of the chest, involving the mediastinum, and was adherent to the adventitia of the large vessels. Jeller and Fisher[3] reported a 4-week-old baby with a polycystic teratoma adherent to the aorta and to the base of the heart. Gebauer[4] removed a large teratoma in a white girl 12 years of age. He undertook a three-step operation. The child had been doing well after the first two stages, but in the last stage the use of a tooth clamp to hold the tumor pedicle made the operation unsuccessful. The tumor was so firmly adherent to the first portion of the aorta that when the latter was caught with the clamp a perforation occurred, with fatal hemorrhage. Beck[5] reported the case of a 22-year-old male, correctly diagnosed and operated upon successfully. Willis[6] described a benign polycystic teratoma of the pericardium in a 10-week-old baby. Claireaux's[7] case was that of a baby, the first of twins, weighing 3 pounds 10 ounces, who was edematous and cyanotic at birth. The mother had had hydramnios during that pregnancy. The tumor was also adherent to the great vessels, and its blood supply was derived from small vessels in the adventitia of the aorta. Somolinos[8] described an intrapericardial teratoma, but we have been unable to obtain that reference.

CASE REPORT

M. S. V. (No. 24298, Río Piedras Municipal Hospital, Puerto Rico), a 15-day-old female infant, was born in the Río Piedras Municipal Hospital of a normal full-term delivery. The baby needed oxygen at birth because of a temporary episode of apnea. Nothing abnormal was observed, and she was discharged on the third day after birth. The baby was apparently well at home until May 26, 1954, when, while drinking a bottle of water, she became cyanotic and dyspneic.

The baby was admitted on May 26, 1954, in a critical condition, with severe dyspnea, coughing, and marked cyanosis. A tentative diagnosis of congenital heart disease was made. The weight was 8 pounds 5 ounces and she seemed fairly well developed. Pul-

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monary expansion was equal. The heart showed slight tachycardia and a soft systolic murmur over the base. There was dullness over the anterior part of the chest. She was placed on oxygen with Alevaire and was started on penicillin (200,000 units procaine daily), which was discontinued on the sixth hospital day.

During the stay in the hospital the child continued to have attacks of cyanosis and coughing. Laboratory reports were as follows: red blood count 5,660,000, white blood count 13,360, hemoglobin 130 per cent. Urine was normal. No other data were obtained. X-ray of the chest on admission revealed: "opacity of the left lung."

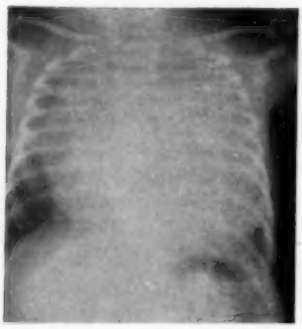

Fig. 1.—X-ray of chest demonstrating mass obliterating the outline of the heart.

The right cardiac border was visualized but not the left one. Additional x-ray studies were made as the baby's condition permitted. An anteroposterior plate of the chest, after a Lipiodol swallow, showed what seemed to be a heart enlarged in all its diameters. The baby was seen by a cardiologist, whose x-ray observations suggested to him a mediastinal mass separate from an apparently normal heart (Fig. 1). Suspecting a tumor of the thymus, the child was given a course of 400 r divided into six treatments, but this was discontinued when the mass was found to be unresponsive to such therapy.

One week before death a bronchogram was done on the left side. It was reported that a cystic mass was present in the center of the left lung. The roentgenologist diagnosed a giant cyst of the lung and an enlarged heart. The thoracic surgeon was consulted, but he postponed surgical intervention because of the precarious condition of the baby. The course was downhill and death occurred suddenly fifty-six days after admission.

Autopsy report (School of Medicine A-2959): The body was that of a well-developed, thin, white female infant about 3 months of age. The main pathological findings were thoracic. A very small, dark-colored thymus was found. The pericardial sac was enormously dilated, occupying about two-thirds of the available space in the thoracic cavity. The lungs were displaced sidewise and backward, most notably the left one; both lungs were atelectatic.

In the pericardial cavity two well-defined masses could be felt, corresponding respectively to a tumor and to the heart. The tumor was situated anteriorly and superiorly to the heart. When the pericardium was punctured, about 150 c.c. of a transparent, amber-colored liquid was withdrawn. When the pericardium was opened, an irregular, bosselated, pearly white tumor was encountered. It measured 7 by 4 by 3 cm., was moderately soft and elastic, and was dumbell-shaped (Fig. 2). The surfaces of the tumor and of the parietal pericardium were smooth, glistening, and devoid of adhesions. Parts of the surface were translucent, corresponding on section with multiple spherical cysts, not larger than 0.8 cm., and containing mucoid, transparent fluid. The intervening tissue was white and glistening.

The tumor was implanted on the adventitia of the aorta, a few millimeters from its origin, through a short pedicle, 0.7 cm. wide, which constituted its only source of blood supply (Fig. 3). The tumor could be displaced slightly against the aortic wall, and its left border was in close apposition with the left auricle. After fixation the tumor pedicle was dissected to study

Fig. 2.

Fig. 3.

Fig. 2.—Thoracic organs removed en bloc. The pericardium has been opened. Note normal size of heart and atelectatic appearance of the lungs.

Fig. 3.—Heart and aorta opened posteriorly after removal. Note adhesion of tumor pedicle on anterior wall of aorta, and compression of left auricle.

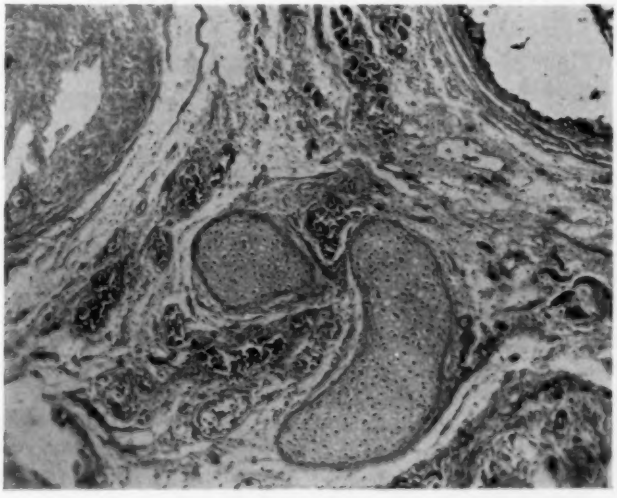

Fig. 4.—Low-power view of histological structure of tumor. Note two islands of cartilage, cystic cavity lined by mucous epithelium, and adenomatous portion resembling salivary gland.

the source of blood supply but no connection with the coronary vessels was found. Some blood vessels from the aortic adventitia seemed to enter the tumor, but their minute size prevented their exact anatomic identification.

Microscopically the tumor was a well-differentiated, polycystic type of teratoma composed of variable epithelial and connective tissue elements, including goblet cell epithelium and the formation of cystic cavities filled with abundant mucoid secretion. There were areas with solid glandular structures resembling salivary gland tissue. The stroma was made up of lax connective tissue, myxoid tissue, smooth muscle cells, and islands of cartilage. All of these structures were well differentiated and orderly (Fig. 4).

The heart was small but normal. The lungs were congested and atelectatic and showed numerous conspicuous large vessels and interlobular septa. There were no cysts in the lungs. The other organs were normal. There was mild congestion of the abdominal viscera.

DISCUSSION

The main symptoms of our case were dyspnea and cyanosis. The chest was more prominent on the left side. A 1-week-old baby in a case reported by Jeller and Fisher had cough and dyspnea since birth, with intermittent bouts of cyanosis. Willis' patient presented symptoms of choking and difficulty in swallowing. The signs and symptoms of pericardial teratoma seem to depend on the size of the tumor and on pressure upon adjacent organs.[9] Tumors close to the great vessels, and which occupy the pericardial sac together with the heart, will produce symptoms earlier than teratomas of the anterior mediastinum, which often are clinically silent until adulthood.

All intrapericardial teratomas previously reported, and our own case, were seen in infants or young children, except Beck's patient who was 22 years of age. This suggests that all or most of the tumors were present at birth.

Operative removal has been attempted and was successful only once to date but seemed possible in our case from an anatomical viewpoint, since there existed a pedicle and a plane of cleavage. However, the operation evidently carries a high risk. The growth of the tumor must have been gradual, considering its benign histological structure and the situs thoracicus which allows progressive accommodation of the expanding mass. Our case presented hydropericardium which was probably due to mild chronic mechanical irritation. Anatomically it is not clear whether the tumor exerted direct pressure on the bronchi or whether the symptoms were due to atelectasis. The ascending aorta appeared somewhat elongated in its intrapericardial portion, but its lumen was unobstructed. The pulmonary artery was likewise unobstructed. There may have been moments when the tumor exerted pressure on these structures, or moments of functional narrowing, since the infant had sudden episodes of anoxia with cyanosis. It must be emphasized that there was no other malformation and that the heart and lungs had developed normally. Our patient, like Claireaux's, derived its blood supply from the aortic adventitia. We favor the viewpoint of Willis and Claireaux that intrapericardial teratoma originates in a similar location and manner as teratoma of the anterior mediastinum, but it is displaced into its unusual position through an unknown mechanism.

SUMMARY

A case of intrapericardial teratoma in an infant is reported, giving a review of the symptoms and signs found, and a pathological description. Only eight such cases have been found reported in the previous literature.

We wish to thank Dr. Enrique Koppisch, Professor of Pathology, School of Medicine, University of Puerto Rico, for his assistance in reviewing the material studied and the manuscript.

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Early IV Therapy

July 26, 1832. The country hereabouts is still agitated with the fear that the Cholera will speedily make its descent upon us in this quarter. Dr. Oliver Blood of Worcester has gone to New York to see how the disease is there treated. His wife read an interesting letter from him in my hearing. He gave an account of the saline injection, a method of cure adopted in Europe. It is done by opening a blood vessel and injecting the solution into the veins. In the case mentioned by him the patient was restored. Fifty ounces were thus injected; and astonishing quantity!

FROM CHRISTOPHER C. BALDWIN DIARY.

Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

First Admission.—A 5-month-old infant boy was admitted to the hospital because of persistent upper respiratory infection of one month's duration, and dyspnea, fever, and productive cough of one day's duration.

The patient had been a normal, full-term infant delivered after an uncomplicated pregnancy and labor. Both parents were said to be in good health, and there were no other siblings. The immediate postnatal period was said to be uneventful. The birth weight was 7 pounds 2 ounces. The patient did not do well from the day of discharge from the hospital where he was born. He began to vomit after almost every feeding in spite of various changes in formula, sometimes in a projectile fashion. He was admitted to the surgical service on the twelfth day of life. Bowel movements had decreased in frequency and amount; the urine had become darker. On examination at that time, a firm, small, intra-abdominal tumor was palpated in the right upper quadrant, but no peristaltic wave was seen. The weight then was 6 pounds 1 ounce. After preparation by intravenous fluids, including plasma, a pyloromyotomy was performed under cyclopropane anesthesia. The tumor was described as being "quite long but very thin." The procedure was well tolerated but the patient had a good deal of postoperative vomiting, which was treated with starvation and gastric suction. Postoperatively, mild icterus was noted but no mention was made of the character of the stool or urine, nor were any laboratory tests carried out. At a follow-up clinic visit about ten days later, the icterus had entirely disappeared, the vomiting had ceased, his appetite was excellent, and he had gained weight—to 14 pounds.

Second Admission.—The patient had apparently been well until about a month prior to readmission, when he developed an upper respiratory infection characterized by coryza and mild cough but without fever. These signs continued unchanged and without accompanying anorexia, vomiting, or diarrhea until two weeks before admission, when the abdomen became protuberant, the stools pale, and the urine appreciably darker. The day before admission he refused his feedings for the first time, and became listless. He was seen by a consultant who referred him into the hospital with a diagnosis of pneumonia.

Physical examination revealed a temperature of 100.6° F., a pulse rate of 148 per minute, and a respiratory rate of 54 per minute. The weight was 10 pounds 4 ounces. The patient was a critically ill, moderately icteric

infant, in marked respiratory distress, with noisy grunting and frothy mucoid discharge from the mouth. He became pallid and ashen during the frequent bouts of coughing. The skin turgor was fair, and the fontanel was slightly depressed. The anteroposterior diameter of the chest was limited in its excursion. There was dullness to percussion over both apices and over the upper two-thirds of the left chest. There were fine crackling râles over these areas and in the right lung, generally. The abdomen was moderately distended. The liver edge was firm and sharp and extended 3 cm. below the costal margin. The spleen was palpated 5 cm. below the costal margin. The abdominal veins were moderately prominent over the epigastric area.

The initial blood hemoglobin was 11.8 Gm. per cent. The erythrocyte count was 4.5 million per cubic millimeter and the leukocyte count 26,600 with a differential count of 60 per cent polymorphonuclear cells and 40 per cent lymphocytes. The leukocyte level never fell below 18,000 per cubic millimeter and the differential remained essentially the same. On the day of death the leukocyte count rose to 72,000 per cubic millimeter, with 66 per cent polymorphonuclear cells. The urine was essentially normal except that the bile tests were positive after the second hospital day and urobilinogen appeared on the ninth hospital day. Nose and throat cultures yielded abundant growth of *Staphylococcus aureus* and *Escherichia coli*. The stools were described as white and formed, with a negative Gmelin test for bile during the first few days. Thereafter they became soft, yellow-white, yellow-green, with a positive bile test on the tenth hospital day. The serum Hinton reaction was negative; a tuberculin test in a dilution of 1:1,000 was negative. The patient was blood group O, Rh-positive. A serum nonprotein nitrogen on admission was 36.9 mg. per cent, rising to 69.2 mg. per cent on the day of death. The serum proteins were 5.5 Gm. per cent, rising to 6.8 Gm. terminally. The serum sodium was 145 and the chloride 92.5 meq. per liter the day before death. A serum sulfadiazine level was 12.5 mg. per cent on admission. Liver function tests shortly after admission were essentially normal except for a one-minute serum bilirubin of 6.2 mg. and a total bilirubin of 11.2 mg. per cent. Four days later the values had dropped to 2.8 and 6.4 mg. per cent, respectively. An electrocardiogram taken on the day before death demonstrated a sinus tachycardia with low T waves in all leads. Roentgenograms taken on admission revealed a diffuse bilateral mottled bronchovascular accentuation alternating with partial lobular atelectasis, but with no frank consolidation. Ten days later, a repeat roentgenogram showed acute overventilation of the lung and definite bronchopneumonia in the right lower lobe.

On admission the patient was placed in oxygen in the steam room and was given large doses of penicillin and sulfadiazine. On this regimen he improved to the point that steam was discontinued, and the sulfadiazine and penicillin were omitted. However, he remained in oxygen because of his rapid respiratory rate and poor air exchange. On the ninth hospital day, the temperature spiked to 100.5° F., and on the following day his respira-

tory difficulty became accentuated. This progressed slowly until death on the eighteenth hospital day. During this period sulfadiazine and penicillin were again given in large doses, as well as streptomycin during the last three days. Over the last nine days of life the icterus was thought to be slowly subsiding. On the day before death the patient became generally edematous and cyanotic, even while in oxygen. Because of this he was given 0.15 mg. of digitoxin intravenously, but this had no effect and the child died on the eighteenth hospital day.

DISCUSSION

DR. CHARLES A. JANEWAY.—This 5-month-old child was a male and was the first-born, both of which facts may be important. He suffered from a complicated illness which I think we have to divide into two phases: First, a neonatal disease, which we can summarize by saying that the child apparently was normal for about the first week of life. During the second week of life he developed vomiting and signs of high intestinal obstruction, with a diminution in quantity of stools, and darkening of urine, which probably suggested dehydration, and he was admitted to the hospital on the twelfth day of life, when a tumor was felt in the right upper quadrant, and consequently was subjected to operation. A pyloromyotomy was performed and the postoperative period was slightly stormy. For the next three and one-half months this child enjoyed good health, he had an excellent weight gain, ate well, and had no disturbances.

At 4 months of age began the second phase, a progressive fatal illness, which ended in about a month. The first signs of this disease were mild upper respiratory symptoms, coryza, and a mild cough without fever. Two weeks later his doctor apparently was sufficiently concerned to start regular administration of a sulfadiazine preparation, which apparently was given in full doses because of the subsequent blood level of 12 mg. per cent.

I am somewhat puzzled with the weight loss. If the child's weight was 10 pounds 14 ounces, this represents a loss of 4 pounds in a few days, which seems somewhat out of the expected range. In any case, I take it that the child had lost some weight. He was critically ill, and the critical symptoms appear to have been respiratory distress and circulatory disturbances. We are told that the child was gasping for breath, breathing rapidly, had poor air exchange, grunting as he breathed, and frothing from the mouth. In addition, he had pallor and an ashy color, which came on with episodes of coughing.

The type of breathing that the child had indicated a severe disturbance of aeration, presumably obstructive emphysema with an overfilled chest, with little expansion. Despite the poor air exchange, râles were heard rather diffusely, so that the child had diffuse signs as shown (1) by the emphysema, presumably due to the trapping of air, as usually occurs in the infantile group of bronchopneumonias or interstitial pneumonias, and (2) diffusely scattered râles and percussion dullness, signs that we usually do not find in the simpler conditions like bronchiolitis, but more often where there is a real infiltrative process, which we can call pneumonia. In addition, the child had a very bad sign, a frothy mucoid discharge from the

mouth, which presumably meant a fair amount of hypersecretion, or transudation of fluid into the respiratory tract, a sign which we associate with pulmonary edema, as it occurs either in severe advanced cardiac failure or as it often occurs in pneumonia with cardiac failure. The other symptoms were related to the abdomen. The examiner was impressed with the distention. The significance of distention in a child like this of course is hard to assess because it is one of the cardinal and outstanding features of pneumonia, when the pneumonia is severe enough to result in anoxia. Icterus, too, is a sign that may merely accompany pneumonia. In adults with lobar pneumonia, icterus, in the days before specific chemotherapy, used to occur in about 10 per cent or better of the patients. It was more likely to occur in an individual with cirrhosis of the liver or some hepatic disease; but it occurred quite frequently in patients with pneumonia alone. The causes of icterus in pneumonia probably are several: (1) in pneumococcal infections at least there is a hemolytic organism with an increased destruction of blood, and, therefore, an increased amount of bile pigment to be dealt with; (2) anoxia, which apparently quite regularly can impair the liver in its ability to deal with bile pigments and excrete them efficiently; (3) in the large areas of consolidation, with large transudation of red cells, you have a large mass of sequestered red cells that are attacked by enzymes and from which the pigments are being absorbed. In children and infants, certainly icterus as a manifestation of pneumonia is far less common. But we certainly have something that might interfere with liver function and unmask any underlying disease which tended toward icterus. In addition to that we have some rather concrete findings: The liver was palpable 3 cm. below the costal margin, and dilated, prominent veins were noted on the abdominal wall. The significance of the enlarged liver is hard to assess because a child with diffuse emphysema, as occurs in a disease like this, almost invariably has a low diaphragm and consequently the upper border of the liver is forced down and becomes more readily palpable. As all of you know, a barely palpable liver is a rather common finding in many normal children, so that we do palpate the displaced liver often in a child who has emphysema. The spleen cannot be dismissed so readily. It indicates that something unusual was going on here, and with the combination of icterus and a palpable liver I think that we have to take the palpability of the liver more seriously than we might otherwise.

The laboratory findings can be broken down into the bacteriologic findings, which were those of many *Staph. aureus* and *Esch. coli* present in the upper respiratory tract. These are organisms that we might well expect to find in an individual given full doses of sulfadiazine. We find them even more frequently today in a child who is given full doses of penicillin. The blood was remarkable for the absence of certain things. In the first place, there was no anemia, despite the fact that this child had apparently been sick for a month and was in the age group where hypochromic, nutritional, iron-deficiency anemia is common anyway, so that a hemoglo-

bin of 11.5 Gm. per cent in this child was certainly not an anemic level. One wonders, in the face of this illness, whether this child was possibly on the way to developing polycythemia rather than anemia, but perhaps limited somewhat by the nutritional supplies available. The hypoproteinemia was not marked either; but it is interesting, despite the progression of the disease, that the serum protein level rose over a gram per cent during the course of the patient's two weeks in the hospital. That could, of course, simply reflect a volume change, loss of water or salt solution from the blood concentration, or it might mean that plasma protein of some type, presumably globulins, was being manufactured at a fairly rapid rate during the last phase of this child's illness. The blood also revealed leukocytosis, despite the lack of fever, and for a child of this age 60 per cent polymorphonuclears is a shift to the left. When you add that to the fact that in the latter phases of the disease, when the child deteriorated, the white count climbed to very high levels and the shift to the left persisted, I think we have to take this finding seriously. The jaundice, in terms of laboratory findings, can only be labeled a jaundice of the obstructive rather than of the hemolytic type. This might be due to intrinsic disease of the liver or it might be due to extrinsic obstruction. In this age group, we have great difficulty in distinguishing between these two, because the flocculation tests, which depend upon abnormal globulins in this age group, do not become positive in the face of even fairly marked destruction of the hepatic parenchyma. The urine was negative, but there was an elevation of nonprotein nitrogen in the terminal phases of the illness. I think with a negative urine all one can say is that presumably this certainly reflected the poor state of general function which this child was in, in later stages of the illness, and possibly a marked breakdown of protein from the stress reaction that certainly must have been present.

Finally, we have the x-ray findings, and I think it might be helpful if the films could be shown now, because they showed a rather extensive pulmonary process, and, as I interpret the reports, changes during the course of the disease.

DR. E. B. D. NEUHAUSER.—The first examination was about two days after the patient came into the hospital the second time, the next examination about ten days later. On the initial examination, the heart and mediastinal shadows appeared to be normal, but the lungs were definitely overdistended, with bulging in many of the interspaces, indicating peripheral emphysema. There were rather streaky, increased densities in the medial third of the lungs and certainly down near the right base—perhaps seen in the next film—alveolar diminution in volume and, I think, early infiltration, probably scattered throughout the rest of each lung.

DR. JANEWAY.—Can you tell about the mediastinal lymph nodes?

DR. NEUHAUSER.—No, I do not think we can either outline them or exclude them. The main feature, I think, is the change in the physiology with the great irregular overdistention of the lungs. The finding in the abdomen which strikes us, and I will throw it in as a red herring, is the seeming promi-

nence of the right upper abdomen; there is slightly more of a bulge here than on the left side, and a little greater thickness and loss of clarity of the normal outline of the soft tissues there. On the lateral film you get a better idea of the great emphysema that is present, and I think now in the second series of films you can see that there is definite lobular atelectasis in the early infiltrative pneumonia throughout the lung.

DR. JANEWAY.—Now as to the child's course during the second hospital stay, apparently there was a moderate degree of improvement in the first nine days when the child was treated by generous doses of penicillin and sulfadiazine. There was a clearing of the icterus, with a fall in the bilirubin levels to about the detectable level of clinical jaundice. This bile reappeared in the stools and urobilinogen began to appear in the urine, which had been absent before, as it does when total obstruction or failure of excretion of the bile into the gastrointestinal tract occurs. Then about the ninth day, however, with a minimal rise of temperature to 100.5° F. the progressive downhill course of the last week began. The child had increasing respiratory distress. Streptomycin was instituted in the last three days, without effect. On the last day cyanosis and edema appeared and despite digitoxin the child succumbed, and the best we can say, I think, is presumably from pulmonocardiac failure of some type.

Did this child have pyloric stenosis, or was the pyloric stenosis some part of the total picture? In favor of pyloric stenosis is the fact that this was the first-born male child, which is the commonest set of circumstances under which this disease occurs. The symptoms on the whole are rather consistent in that the child was well for the first week and then began to have forceful and projectile vomiting; it was associated with evidences that less material was getting through the pylorus (i.e., he was becoming dehydrated), then, finally, and best of all, a tumor was felt, and operation relieved the child's symptoms. Unusual facts are that, first, this began early (most children with pyloric stenosis do not get into trouble until about 3 weeks of age rather than in the second week of life); second, no peristaltic waves were seen across the upper abdomen; and third, the note about the tumor just suggests that possibly it was somewhat unusual. I am inclined to believe that this child did have pyloric stenosis. If so, what connection could exist between this episode and the later illness? Was this icterus in the postoperative period a warning flag of some sort? Did it indicate there was something about this child's liver that made him unable to deal well with bile pigments under stress?

Did this child have a transfusion or any other procedure during the period of his second illness? The time intervals for that are certainly consistent.

DR. MAURICE OSBORNE.—He received 30 c.c. of plasma in the immediate preoperative preparation.

DR. JANEWAY.—I think it is worth pointing out that there are means other than blood plasma of getting serum hepatitis. But we think we have plugged most of those loopholes in this hospital because we do use auto-

claved finger-pick needles, individual ones, and do not allow individuals to go from patient to patient in obtaining blood counts with a stylet which is improperly sterilized between each puncture. We use autoclaved syringes and needles entirely and hepatitis should not occur, but the fact that this child received plasma does raise the possibility. Plasma in our hospital is no more dangerous than blood because for quite a long time we have used only single unit, compatible plasma, which is cross-matched just as blood, rather than the pooled plasma, which does not have to be matched with the patient's blood group. We do this just to avoid the pooling, which increases the statistical chances of transmitting this disease by the number of donors included in the pool.

What sort of process, then, was the final illness that killed this child? I think we have to admit that the respiratory picture was the prominent one; but we cannot discount this jaundice and large liver and spleen. What possible interpretations can we place on a progressive, fatal, pulmonary disease? Was it a respiratory infection producing emphysema and pneumonia, going on to failure to resolve with interference with blood flow through the lungs and finally cor pulmonale with failure? The type of failure to which this patient succumbed is quite consistent with that, in that on the last day the child developed generalized edema, which would be consistent with congestive failure of the right-sided type with failure of the right ventricle. The cyanosis certainly could be explained by his respiratory situation. Or, was this respiratory infection, in which cardiac failure played a considerable role, from early in the disease? The presence of the large liver and the pulmonary edema, with frothy sputum, makes one wonder if this child's heart was not performing well from the beginning. The heart is not mentioned on the physical examination, but we know that it is almost impossible to examine the heart satisfactorily in an emphysematous child. You cannot percuss it or tell what size it is. On the films that Dr. Neuhauser showed, however, the heart appears normal, so that at least we do not have massive enlargement or dilatation, which is certainly against the cardiac factor being a very important one, except at the very end of the disease. It seems unlikely that the child had congenital heart disease, certainly not with any type of shunt. But there are various acquired conditions that affect the myocardial function in infancy, and we have obscure cases of myocarditis in which the children come in with pulmonary edema or often superimposed infection and a poorly functioning heart. There is usually marked cardiac enlargement under those circumstances. We know that sulfonamides, in some individuals, have led to granulomatous changes in the heart and myocardial failure. We know that anoxia affects the function of the myocardium and the usual patient who dies of pneumonia certainly has cardiac and circulatory failure in which anoxia must play a major role.

Finally, could this child have had some sort of primary pulmonary vascular disease in which the blood flow through the lungs was compromised by the vascular process? That might produce a type of cardiac enlargement that would not show too readily

on films because it tends to be in an anteroposterior direction rather than out to the left. Certainly, failure of the right heart can come quickly when real obstruction to blood flow through the lungs occurs. In a group of patients described by Hamman and Rich[1] some years ago, patients died in two months from the onset of the pulmonary infection, which presumably initiated the interference of blood flow in the lungs from fibrosis.

If this was an infection, which I personally believe it was, with the leukocytosis, despite the lack of fever, with the general physical signs and the leukocytosis which the child exhibited, then why did the child fail to respond to treatment? On the one hand, perhaps the type of infection was one that would not respond to the type of treatment administered. Here is a child who received only sulfadiazine prior to admission, and who received only penicillin and sulfadiazine up to the last three days of life. We know that there are organisms which this combination of therapeutic agents used in 1948 might not deal with well today. At the top of the list I think we would have to place the staphylococcus, which in this case may have responded well to penicillin in the first period and then have developed resistance and in that way explain the sudden change in the course of the disease after nine days in the hospital. We might be dealing with other types of infections, fungus infection, or tuberculosis, though that is probably ruled out. A negative tuberculin test in dilution of 1:1,000 is not conclusive proof. Fungal infection is rare except in a child with some underlying serious disease with a long period of chemotherapy.

We might look then on the other side of the picture, to what may be wrong with the functioning of an organ to cause trouble. The individual with bronchiectasis, for instance, cannot clear his secretions, and if he gets exogenous infection these do not drain well and the child becomes sick. We might have an anomaly, but we have no evidence of a specific asymmetric area where infection is remaining, which we see with anomalies of the bronchi. There may be scarring from some cause, which seems unlikely at this early age, or aspiration of foreign material in a child who had vomited a good deal, which in turn may have led to some pulmonary fibrosis and then poor pulmonary function in the face of infection.

We might have mucoviscidosis in this child with pulmonary disease that does not respond well. We know that the liver occasionally is involved in this process. Could he have obstruction of the bile ducts and obstruction in the bronchi on the basis of thickened secretions due to mucoviscidosis? I think the main point against that is the excellent weight gain the child made in the period between his two hospitalizations.

We have learned in recent years of a group of disturbances of the immune mechanisms occurring in children, characterized by failure to produce antibodies adequately, which we call agammaglobulinemia of the congenital type. In that situation the deficiency is in the plasma cell series, so that they do not synthesize antibodies in response to stimulation. How could we tell about that? We cannot without further information than we have, and actually this child was seen before we had recognized

such a disease. The only two children we have had who died in this age group with this disease had diarrhea as a rather outstanding manifestation, presumably because of inability of the bowel wall to protect itself. So the absence of diarrhea in this child is perhaps against that diagnosis; but I think it is perfectly conceivable. A child with this disease, however, usually develops an overwhelming septic blood stream infection, when he gets a pyogenic infection, so that the clinical picture is not what I would expect in an agammaglobulinemic child. The fact that this child is a male at least makes it possible, but we have no data on which we can go here. It is reported that the child was group O Rh-positive. If the child had agammaglobulinemia we would expect him to have no anti-A and anti-B agglutinins in his blood serum. I do not know whether or not that was tested; it probably was not at this time.

Also, there is a mysterious group of cases which several of us have been interested in, in which the child, for reasons that are obscure, has actually developed a hypergammaglobulinemia,[2] and in which resistance to infection, particularly of this sort, has been rather striking. They have almost all suffered from chronic and persistent infections due to staphylococci, proteus, pyocyaneus, and these ordinarily relatively banal organisms, which have been very resistant to treatment. The child affected seems to have too many plasma cells. We have at least one child, very much like the child we are discussing, who, however, has lived to 3 years of age now, and who has a large liver and spleen, emphysema, chronic cough, chronic pulmonary infection with *Staph. aureus.*

The underlying cause in this case may not be an infection at all. What other conditions could give this picture? Certainly some types of generalized neoplasia could, but the findings do not fit with any of the neoplastic processes I know anything about. Of course, one always must think of leukemia or lymphoma in a child who behaves this way. It might be Letterer-Siwe's disease, but the pulmonary infiltration seems too soft and the signs of infection in the lungs too great, to fit with that type of process. We have the disease "idiopathic pulmonary hemosiderosis" in which pulmonary fibrosis develops, but those children usually have anemia and are older by the time they get in serious trouble.

There are many possibilities here and it is hard to put them together into one diagnosis. The jaundice still bothers me. If the jaundice had been progressive I could account for it, perhaps, as cholangitis, or something of that sort. But it is hard to conceive of enlarged glands coming up and then going down and releasing the obstruction and producing severe and complete obstruction originally. It certainly does not happen very often. With a septic type of infection and secondary icterus you usually do not have clay-colored stools and signs of obstruction. It almost makes me wonder if we have to make two diagnoses, first, a chronic pulmonary infection, presumably due to *Staph. aureus,* and second, a hepatitis arising from the plasma transfusion at the first admission. I frankly cannot make a diagnosis. If I had to give my choice as perhaps the most likely diagnosis, I would say that this child

had a chronic staphylococcal pneumonia. He perhaps is one of this obscure group of children whom we have tied together by the fact that they have hypergammaglobulinemia and rise in their serum proteins. The fact that this child's serum protein rose 1.3 Gm. in about two and one-half weeks suggests that may be the situation here. I believe also that Dr. Craig is going to find much more in the lungs than the x-ray films suggest, with a great deal of fibrosis and infiltration and the presence of many mononuclear plasma cells and polymorphonuclears in the exudate. Possibly we have here as a complication of the initial operation a relatively mild but definitely viral type of hepatitis of the homologous serum jaundice type.

Dr. Sidney Farber.—Thank you, Dr. Janeway. This exhaustive discussion is now open for further comment. Dr. Davies, would you like to offer an opinion?

Dr. John H. Davies.—I am under the disadvantage of having discussed this case previously. All I can say is that a basic metabolic defect was present.

Dr. Cannon Eley.—I would like to know whether this child ever had positive blood cultures? That is, whether instead of mechanical jaundice, he had a hemolytic type of jaundice from bacterial sepsis.

Dr. Osborne.—Blood cultures were not obtained.

I wonder if it would help Dr. Janeway to know that the child lost weight steadily throughout the second hospitalization.

Dr. Janeway.—That information does not help much. I frankly am confused by this child, who, it was clearly evident, was very sick.

Dr. Neuhauser.—One other disease that Dr. Janeway did not mention and that might be considered is central autonomic dysfunction (Riley-Day syndrome). Of course, with that syndrome there are other features of failure, tear formation, corneal ulcers, and vasomotor disturbances.

Dr. Farber.—Dr. Neuhauser, do you have barium studies on the pylorus?

Dr. Neuhauser.—They were not done.

Dr. Farber.—Is it customary to do so?

Dr. Neuhauser.—No. The clinical picture is clear and the tumor was felt in this case.

A Physician.—Dr. Neuhauser, does the Riley-Day syndrome affect the pylorus?

Dr. Neuhauser.—I do not see why. I think the pathologists have been rather lax in telling us the nature of pyloric stenosis. It certainly has become quite clear recently in many adults that the degeneration of the ganglion cells leads to the whole trouble.

Dr. Farber.—Dr. Craig, would you give the findings and would you also give the justification for taking this case up a second time?

Dr. John M. Craig.—Frankly, I have no justification. I had forgotten that it was previously presented. I ran across it in looking for other things and it seemed to be a delightfully complicated and difficult case.

This child, at autopsy, had a small amount of edema, predominantly of the face, and a small amount of fluid in the peritoneal cavity. There was little else to suggest cardiac failure. The heart was not enlarged, nor was the right ventricle dilated. The lungs were both abnormally heavy. They showed, grossly, areas of emphysema, atelectasis, and frank pneumonia. The lungs almost met in the midline, anteriorly. The bronchi were filled with a large amount of thick, tenacious secretion (Fig. 1). The secretion in the bronchi could be traced as mucous plugs, fairly far out into the alveoli, and was occasionally associated with proliferation of the alveolar septal cells. The spleen was about 50 per cent over the normal weight. Well-formed secondary reaction centers were demonstrated with great ease. There was no increase in the number of plasma cells or lymphoid nodules, nor was there evidence of excess lymphoid tissue in the lungs such as we have seen in cases of hypergammaglobulinemia of which Dr. Janeway spoke. The presence of these reaction centers and of the plasma cells in the spleen, I think, fairly well eliminates the possibility of agammaglobulinemia.

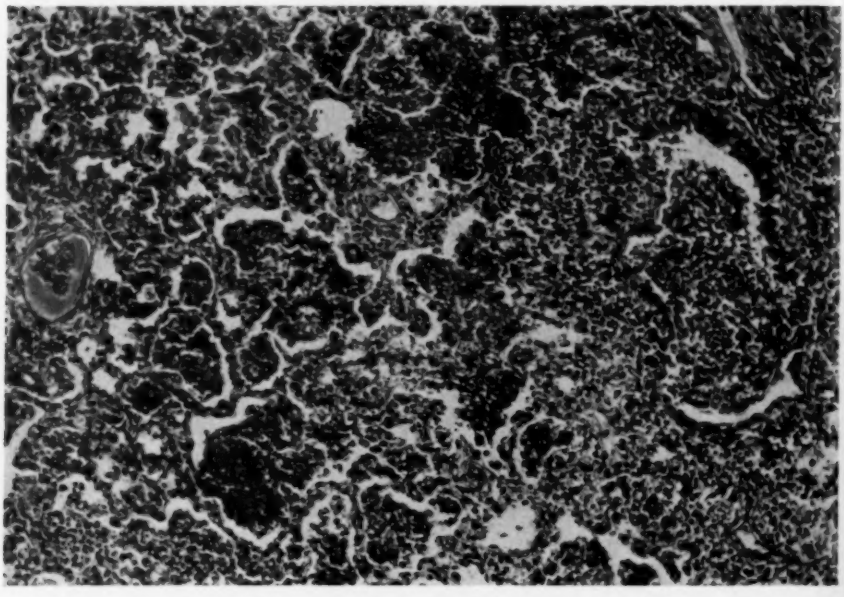

Fig. 1.—Lung. The bronchiole is dilated and filled with a purulent exudate. There is a purulent exudate in the alveoli. (Hematoxylin and eosin; ×130.)

The pylorus was slightly thicker than normal, and no healed incision was demonstrable. The ganglion cells appeared normal in number, with no evidence of degeneration. The musculature was not obviously hypertrophied.

The liver was slightly irregular on the surface and the lobular pattern

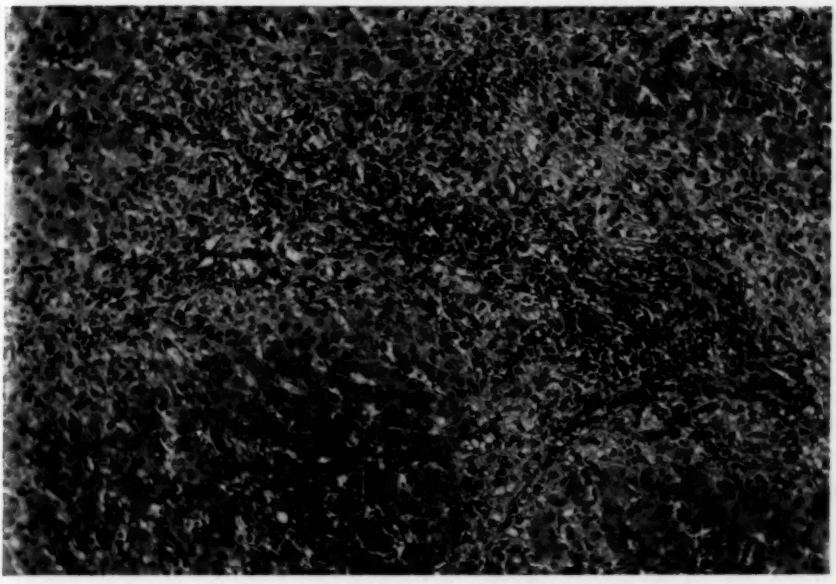

Fig. 2.—Liver. The portal triad is widened and infiltrated with inflammatory cells. There is beginning isolation of liver parenchymal lobules. (Hematoxylin and eosin; ×150.)

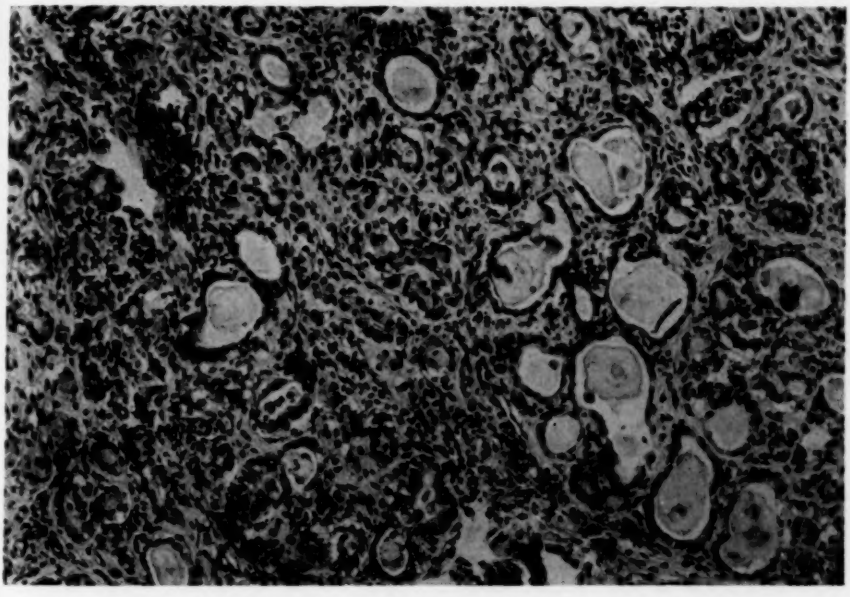

Fig. 3.—Pancreas. Marked loss of acini, fibrosis, cyst formation, and inspissation of pancreatic secretions are present. (Hematoxylin and eosin; ×150.)

was slightly accentuated. Microscopically, the portal areas were greatly broadened, and there were many bile ducts containing large reddish-brown plugs of inspissated bile (Fig. 2). There was a good deal of inflammation in the portal areas, consisting of polymorphonuclear cells and lymphocytes. The parenchyma had no fatty infiltration, nor was there degeneration of the hepatic cell. The pancreas was not grossly abnormal, but on microscopic examination showed the typical findings of pancreatic fibrosis, with marked destruction of the parenchyma and large inspissated plugs of mucus in the ducts and in the remaining acini (Fig. 3). We believed, then, that this child had as the primary underlying disorder, generalized mucoviscidosis. We did not find much evidence of cardiac failure. Even in children who do have some evidence of hypertrophy of the right heart, evidence of right heart failure is comparatively uncommon. Nadas, Cogan, Landing, and Shwachman[3] gathered thirty-five cases in which they thought there was some significant pathologic increase in the size of the right heart, and in only two of those, as I remember, was there clinical evidence of cardiac failure. The changes in the lung, as has been brought out here many times, were undoubtedly related in part to the obstruction caused by the increased viscosity of the mucoid bronchial secretions. The changes in the liver were in large part consistent with those seen in cases of pancreatic fibrosis. Of about ninety autopsies of pancreatic fibrosis we have had five or six cases with sufficient fibrosis and alteration of the lobular pattern to designate as cirrhosis. These cases have a characteristic pattern of proliferative bile ducts filled with large opaque inspissated bile plugs. The lesion is a very focal one; there may be broad areas containing many lobules without any pathologic alteration, except for an occasional inspissated bile plug. In other areas one sees the pattern displayed here, with very broad portal areas, many proliferative bile ducts, and large inspissated plugs with bile in them. In only two of the five or six cases that I mentioned was there significant jaundice or other evidence of cirrhosis, so the cirrhosis is a silent one.

Belding and Kernohan[4] have studied the pylorus of a group of patients with pyloric stenosis by serial section. Some of these were young infants, up to the age of 5 months; others were adults who as infants had had gastrojejunostomies because of pyloric stenosis. They described minor changes in the ganglion cells and the nerves in the pylorus; they were not able to demonstrate any pathologic alteration in the muscle proper. The changes they describe are qualitative ones only. They do not show the absence of ganglion cells as is found in congenital megacolon. It appears doubtful whether the alterations they describe are pathognomonic for pyloric stenosis.

DR. FARBER.—It would be of interest to some of you to read the paper written in 1908 by John Lovett Morse,[5] who at one time was professor of pediatrics, Fred Murphy, who did child surgery, and S. B. Wolbach. They described a child on whom the operation of gastrojejunostomy was performed because of pyloric stenosis and who died six and one-half months later. The interesting part of the story is that the tumor still persisted.

It was just as large as ever, and the gastrojejunostomy did not cause any change in the condition. Yet this is not the first time, is it, Dr. Craig, that we have not been certain about whether or not a pyloromyotomy had been performed after an unquestioned operation?

DR. CRAIG.—I can remember at least one other such case.

DR. FARBER.—The healing is quite complete, but the tumor disappears after a short time and does not return. I would be extremely skeptical, too, of the importance of the ganglion cell changes having any primary importance here in the causation of pyloric stenosis. We certainly have added nothing to our knowledge of the nature of the disease, Dr. Neuhauser, in all the years that it has been studied in so many, many patients, so far as the causative factor is concerned. In looking over the story with great care, again, and afresh, I think the only clue whatsoever to the pancreatic part of this picture is the fact that the child had *Staph. aureus* infection of the lungs with hyperexpansion. While it has been emphasized by Dr. Janeway repeatedly throughout his talk and by Drs. Davies and Neuhauser that we must look for an underlying basic defect for the child's clinical picture, I think it is worth while emphasizing that we have had many instances of staphylococcal pneumonia without any involvement of the pancreas or without an underlying disease that we were able to recognize. The x-ray picture, which is so characteristic of marked mucoviscidosis, is rarely produced in our experience by any other underlying condition, and I think that that probably is the most significant clue here. Dr. Janeway did bring out the fact that there was no strong nutritional story here. There were lacking here the foul or the characteristic celiac-like stools. There were lacking many of the other features of the characteristic full-blown mucoviscidosis. Had the child lived longer, I think there would have been abundant opportunity for all of that to have developed.

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Medical Progress

PRESENT STATUS OF RADIOISOTOPES IN PEDIATRICS

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RADIOISOTOPES can be used safely in children, although they are more useful for diagnosis than for therapy. When I first used them in children in 1938, it was with the hope that they would eventually be very useful therapeutically, and also particularly in the difficult diagnostic problems of intermediate metabolic pathways. The goal remains the same and the aspiration of many investigators and clinicians continues to be realized with their use.

For diagnostic purposes adequate tracer doses are far below the injurious dosage. Originally, the principal objections to their use were the possibility of overirradiation and ultimate malignancy. The dosage, however, must be exact so that general irradiation is below the accepted tolerance dose but in sufficient quantity in the body to be counted accurately.

Regarding possible ultimate serious sequelae: strontium ($Sr.^{90}$), plutonium (Pu), and gallium (Ga) are too harmful to be considered useful in human beings. Radium and thorium have been followed by development of cancer. Now, after eighteen years of therapeutic usage, proved instances of malignancy have not been reported when approved doses of radioisotopes have been given. This is of practical importance when one considers, for instance, that a number of children with carcinoma of the thyroid receive large radiation doses of I^{131}. The same is true generally of numerous adults treated with a variety of radioisotopes. However, Seidlin and associates[1] reported that out of sixteen adults treated with large doses of I^{131} for thyroid carcinoma, two developed myeloid leukemia (one received 1,455 mc. in four years and the other, with possible leukemia at the start of therapy, received 1,600 mc. during five years). In these cases, such large doses were probably justified.

The tracer dose of I^{131} for children is far less: 5 μc for the thyroid is sufficient. If roentgen irradiation of children is considered necessary for diagnostic purposes, there should be no fear in using isotopes in less or equal radiation dosage. This does not, of course, imply approval of uncontrolled radiographic exposure. Duffy and Fitzgerald[2] have commented upon the subsequent development of thyroid carcinoma in children years after x-ray therapy for thymic enalrgement. Such dosage is usually about 100 to 300 roentgens (r).

It may well come to pass that within five to ten years radioisotopes will be universally acceptable by clinicians for proper usage in children.

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DIAGNOSTIC APPLICATIONS

The ideal use of radioisotopes is the employment of an isotope of an element which localizes in a separate organ because it is used there only. Furthermore, its energy (quantum energy, designated as milliequivalent electron voltage—mev) should be safe for that organ and the energy easily measureable. The concentration achieved, the physical half-life, the rate at which it leaves the organ and the body, as well as the energy of its radiation (mev) determines the local tissue dose produced.

The 101 known elements have about 1,100 isotopes, of which 200 to 300 are stable (nondisintegrating) and 600 to 800 are radioisotopes (disintegrated by radiation). There are nineteen elements in man and fifteen have radioisotopes safe for human beings: I, P, Na, K, C, Ca, Mg, Mn, Cu, Zn, S, Fe, Co, Ni and H. I^{131} was the first isotope used for clinical diagnostic studies and no other radioisotope has such ideal properties for the study of thyroid or other medical problems. It is given to children usually in oral doses of 5 μc or less. Such small doses can be used if one measures the gland with a scintillation counter rather than a Geiger-Mueller counter (Fig. 1). With a gamma-sensitive Geiger counter, I^{131} can be measured with 10 μc, while with the use of a scintillation counter 1 or 2 μc suffices, and 5 μc is generous (5 μc, if 50 per cent is taken up in a 5 gram thyroid, gives a tissue dose of about 50 rads.*).

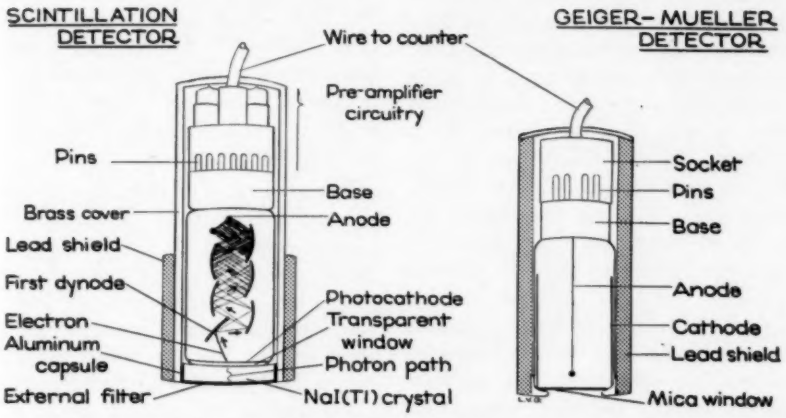

Fig. 1.—A scintillation detector consists of a crystal, commonly sodium iodide thallium (Tl) activated, a photomultiplier tube and an amplifier circuit. The crystal and tube are kept "light-tight," usually with metal. A lead shield reduces the background of cosmic radiation. Gamma radiation striking the crystal generates photons (light), these going into the photomultiplier, setup electrons from the photocathode; these electrons are reflected from the multiple dynodes in the tube, thus multiplying the original photon by a factor of about one million. The preamplifier further raises this current high enough for the distal counter to record these charges. The gamma radiation from I^{131} is detectable by a scintillation detector during in vivo counting of the glands. The beta radiation of I^{131} is absorbed in the thyroid, and too little leaves the gland for external counting.

*This is calculated as follows: 5 μc × 50 per cent equals 2.5 μc in thyroid. If the thyroid weighs 5 grams, the concentration is 0.5 μc per gram. The physical half-life of I^{131} is 8 days; the gammas usually emanate outward and the betas stay in and give 140 rads per μc per gram. If excretion reduces half-life to 5 days (the biological half-life), the total dose in the gland is 5/8 × 140 × 0.5, or about 50 rads. The roentgen unit refers to exposure; the rad refers to tissue absorption.

I^{132} is probably more benign (2½ hour half-life) and is used when large activities for a brief test are required or when repeat tests are to be done at short intervals. However, it is less convenient and more expensive than I^{131} since it is shipped as tellurium (Te^{132}), from which I^{132} must be separated shortly before use.

Tracer doses can be given intravenously, but this is usually unnecessary and somewhat impractical. The dose can be sucked from a small medicine bottle through a straw, then twice-filled with water and drained again by straw to reduce the contents to a minimum in order to quantitate accurately by a detector. The test should not be carried out until the patient has discontinued the following substances for the stated times, for they block the gland from taking up the I^{131}: thyroid substance for one to two weeks; iodides for three to six weeks; thiourea compounds for one week; iodinated radiographic compounds for at least several months. Iodinated compounds given for radiographs will sometimes localize for long times. If any Lipiodol remains in the chest or the spinal column it will sometimes suppress thyroid uptake for months or even several years. Other commonly used materials which block uptake to various degrees, and often totally, are the various sulfonamides, Mercuhydrin, and fish meals. Brassica vegetables such as turnips, rutabagas, and cabbage usually suppress uptake only if ingested in large amounts over long periods.

Normal measurements after oral administration are: at 6 hours, between 4 and 22 per cent; at 24 hours, between 7 and 35 per cent. Any higher or lower value is strongly suggestive of hyperthyroidism or hypothyroidism. Uptakes of 0 to 1 per cent are indicative of nonfunctioning thyroid tissue or, more often, athyreosis. In hyperthyroidism uptake is sometimes over 90 per cent.

This test is safe, simple, quickly done, reproducible, and not painful. We think it is very reliable—probably more so than a blood cholesterol or a B.M.R. When protein-bound iodine or butanol extractable iodine tests are reliably done, the thyroid uptake of I^{131} is no more accurate or informative. As with other thyroid function tests, there is often an overlap in the uptake test between values of euthyroidism, hypothyroidism and hyperthyroidism.

The amount of thyroid hormone can be approximated by measuring the plasma counts of I^{131} by the method of Scott and Reilly.[3] Plasma is separated by centrifugation at twenty-four or forty-eight hours after the start of the test, at which time the iodine has passed into the gland and reappears in the plasma as protein-bound material, presumably as hormone. This I^{131}, still in the inorganic form, can be adsorbed on anionic resin. The measured activity of this inorganic iodide is subtracted from the total activity of the plasma. The remainder of activity is protein bound I^{131} and is expressed as counts per second per cent and as per cent of iodide converted.

Another method of measuring conversion by the gland of inorganic iodide into organic iodine (persumably hormone) has been devised by Scott and associates.[4] Five to 10μc I^{131} is given orally. Inorganic iodide in the blood stream is principally in the red blood cells and that iodine in the plasma is organic. They measure these two fractions and express the conver-

sion by a ratio and by per cent. Others have worked out conversion ratios by different mathematical procedures. The Scott and Reilly method seems a more simple way than either the partition of iodide activity between cells and plasma, or the Somogyi, or the trichloroacetic acid protein precipitation methods.

Currently, I^{131}-tagged human serum albumin (IHSA) is considered the best preparation for localizing brain tumors. I^{131}-tagged diiodofluorescein was the first compound used for this purpose. The increased vascularity of the tumor favors localization of the tracer though, in general, these tumors are quite accurately localized by a complete history and the combination of neurological examination, air injection, and carotid angiogram. Occasionally IHSA is helpful in detection before operation,[5] particularly in "silent" area; to help the operator further P^{32} can be injected intravenously during surgery in order to localize more accurately with a needle probe counting detector.

Liver function can be tested by iodinated (I^{131}-tagged) rose bengal. It is claimed by Taplin and co-workers[6] that the tagged rose bengal test is far more sensitive than the usual liver function tests. This could be significant and it is hoped that other investigators can corroborate this claim.

Another promising use for I^{131} is found in the report of Lavik and associates[7] in which pancreatic protein digestion is tested by ingestion of I^{131}-tagged calcium caseinate, the thyroid uptake blocked by Lugol's solution, and observation made as to whether fecal excretion of isotope is above 6 per cent (normal). In cystic fibrosis of the pancreas, tagged protein remains undigested and 10 to 40 per cent of the activity appears in feces. Detection of lower than normal amounts of I^{131} in blood and urine is further confirmation, but not essential. The tagging of proteins does not seem to alter them as substitutes for enzymatic or immunological tests. Lavick's test seems more practical and simple for the diagnosis of pancreatic cystic fibrosis than passage of a tube to the duodenum under fluoroscopic control, by chemical examination of duodenal contents, or by testing the trypsin digestive power of the stool on gelatin in x-ray film.

Many compounds can be tagged with I^{131} or P^{32}, making it possible to trace them in the human body and leading to the practical investigation of many obscure problems in children. I^{131} is quite safe to use and easily measured. P^{32}, having no gamma, is more difficult to measure in patients; also, it goes to the bone marrow, which is radiosensitive and may be injured easily.

Other uses for iodinated compounds are the measurement of cardiac output and blood volume. IHSA has been used often to measure plasma volume but occasionally gives misleading high values due to the leakage of tracer into the thoracic duct or urine. Cr^{51} makes an excellent tag for red cells and stays in them very well (about 1 per cent of it is leeched daily). By measuring either plasma volume or red cell mass, the total blood volume is then calculated from the hematocrit value.

P^{32} has been used extensively to localize tumors in the body, especially in the brain. Since little of its beta radiation gets to the surface, and clinical detection has to be by bremsstrahlung radiation, which detection is difficult, P^{32} is now seldom used. Moreover, P^{32} can be localized in many areas

other than the tumor, e.g., normal lymph nodes and areas of inflammation.

Tagging red blood cells with Cr^{51} as $Na_2Cr^{51}O_4$ is useful for measuring blood volume as well as for the determination of red cell life. The tracer is eluted very slowly from the red cells, and the doses required are not harmful. Reilly and co-workers[8] described a good method for measurement of blood volume. Whole blood (5 to 10 c.c.) is shaken gently with the tagged sodium chromate (40 μc is enough for adults, 20 μc for children), then centrifuged. The plasma is drawn off by pipette to carry away the unbound Cr^{51}. The red cells are then suspended in saline and reinjected into the patient. Complete mixing occurs in about ten to fifteen minutes in the normal patient. One to 5 c.c. of blood is then withdrawn for scintillation crystal counting and compared with a standard. To compute red cell life, samples of the patient's blood (1 to 2 c.c.) are taken every few days thereafter and measured against the value of the original tagged sample. Corrections are made for the small loss of Cr^{51} from cells.

Na^{24}, another commonly used radioisotope in adults, has not been used often in children. It is useful for measuring circulation time in limbs where one suspects impaired circulation or arteriovenous shunts, for electrolyte exchange between circulation and ascitic fluid and urine, for determination of sodium space in children,[9] and for cardiac diagnosis, prognosis, cardiac output, and stroke volume.[10] One of the earliest reported uses of this radioisotope in children was that by Hubbard and collaborators[11] in 1942, who determined the velocity of blood flow by injecting Na^{24} intravenously in one arm and timing its arrival in the opposite arm.

Fe^{59} has been helpful in determining iron requirements, iron turnover in plasma and liver, hemoglobin production, red blood cell production and its life span. Difficulties in determining red cell life by Fe^{59} are that red cells must be labeled biologically to obviate the possibility of using the patient's own cells and, also, that the Fe^{59} is reutilized.

Potassium (K^{42} and K^{43}) combined with Na^{24} is useful for intra- and extracellular fluid studies.

B_{12}, tagged with Co^{60}, given orally, is helpful in the diagnosis of pernicious anemia of adults. If the necessary intrinsic factor from the stomach is not present the B_{12}-Co^{60} will not be absorbed quantitatively, as revealed by low urinary and high fecal excretion of the Co^{60}. It is possible that this text might be applicable in the study of megaloblastic anemia of infancy.

THERAPEUTIC APPLICATIONS

There are about 300 isotopes which might be considered for therapy but each of them presents different physical, chemical, and biological problems which have to be considered before their employment can be determined as safe or useful. In childhood the radioisotopes which are more commonly employed therapeutically are I^{131}, P^{32}, colloidal Au^{198}, and colloidal P^{32}.

I^{131} can be used in hyperthyroidism, certain carcinomas of the thyroid, and for medically intractable cardiac decompensation. In private practice it is not yet acceptable therapy to treat a hyperthyroid child with I^{131} because we do not yet know about carcinogenesis in the thyroid, and ovarian suppression and depression of the hemato-

poietic organs are to be considered as possibilities. In my opinion this disease in children, when severe and of long duration, is best treated by thyroidectomy (subtotal). If toxicity is mild, treatment should consist of thiouracil drugs, iodine, bed rest, sedation, etc., even though it required months of time. If there is a relapse after surgical treatment, I^{131} will usually be effective. I^{131} can be given to those patients where one does not dare to operate because of high risk (e.g., cardiac decompensation). In such a case 2 to 6 μc I^{131} in one oral dose is sufficient. The production of an enduring hypothyroid state might be considered advantageous in cardiac patients.

Carcinoma of the thyroid in children usually lasts many years before death occurs and many such patients live a fairly comfortable life. Nevertheless, many respected authorities feel these children should be treated with I^{131}, and even vigorously, if there is any indication of uptake with metastases. Only alveolar or follicular types occasionally take up iodine, while the papillary and anaplastic types do so very rarely. The thyroid gland and all dissectible metastases should be removed surgically. The remaining metastases may then mature sufficiently to take up I^{131} even if they had not done so previously. If they do not take up I^{131} sufficiently, the following procedures may be tried: administer thyrotrophic stimulating hormone (TSH) daily for one to two weeks, or give generous doses of thiouracil drugs daily for one to two weeks. Within twelve to twenty-four hours after discontinuing these priming medications for metastases, give a test dose of I^{131} (250 to 1,000 μc) in order to produce sufficient counts above body background counts to detect possible uptake by metastases. A scintillation counter ought to be used, since Geiger counters are too inefficient for recording gamma rays in vivo for detecting metastases unless large quantities of radioisotopes are given.

The total I^{131} excretion in the first twenty-four- or forty-eight-hour urine can also give a clue. Since the child's thyroid is removed, 80 to 85 per cent of the I^{131} should be excreted in the first twenty-four hours. If the amount is less, one can be suspicious of metastases which are taking up the I^{131}. These stratagems do not often succeed if thyroidectomy and ablation of remaining thyroid tissue by I^{131} have not already succeeded. Months after removal of thyroid tissue, some of these metastases start to show I^{131} uptake.

If a thyroidectomized child does not develop extreme hypothyroidism, it is possible that there is physiologically active thyroid tissue elsewhere (metastatic tumor). In this condition we have given several children 25 mc. of I^{131} orally at monthly intervals for several months as a therapeutic dose. Ideally, such doses should be repeated until there is no further evidence of uptake or retention and at least 95 per cent of the dose is accounted for in a forty-eight-hour urine specimen. When all evidence of uptake disappears, four to six months should be allowed before rechecking with a tracer dose. One patient with thyroid carcinoma was observed by us for twenty-one years and treated successively by surgery (ultimately not successfully), roentgen irradiation, then with I^{131} for five years when a young adult. During I^{131} therapy, chest metastases disappeared, and he com-

pleted his education and was happily employed until cancer finally caused his death.

I^{131} therapy is also helpful in chronic intractable cardiac decompensation. It reduces the basal metabolic activity and spares the heart. One should avoid a dose that will lead to marked myxedema; rather, moderate hypothyroidism should be the aim. In this state, patients are more comfortable, have less frequent and less severe attacks of dyspnea, fluid retention, and precordial distress. To reduce the function of these euthyroid glands, the dose of I^{131} usually is three to four times that total required for hyperplastic glands. Doses of 2 to 4 mc. can be given at weekly or monthly intervals until clinical observation and measured uptake in the thyroid gland show a definite degree of mild hypothyroidism. Usually one to three such treatments are required. Maximum effect usually appears four to eight weeks after the I^{131} dosage. If the final state is too low and uncomfortable for the patient, small doses of thyroid substance will rectify it.

P^{32}, a beta emitter, localizes principally in the liver, spleen, and bone marrow and has a vigorous effect, especially in leukemic tissue. P^{32} follows the metabolic pathways of phosphorus and becomes bound as P^{32} nucleoproteins, etc., in the body. Because of the higher synthesis rate of malignant cells, relatively more P^{32} is found in these cells, and for this reason it may be used in therapy. The localization of P^{32} in the endosteum also makes it possible to depress bone marrow. P^{32} is indicated particularly for polycythemia vera and is more acceptable than repeated phlebotomy. A single dose of 1 to 2 mc. may be all that is needed for months or a year at a time.

Chronic leukemia responds quite favorably to P^{32} in a dose between 1 and 2 mc. for children, preferably by the intravenous route, though it can be given orally. The objective in leukemia is to keep the body content at about 1 or 2 mc. of P^{32} so that fractional doses are given every three, five, or seven days, calculated upon the decay and excretion of P^{32}. Usually the saturation of the body by 1 to 2 mc. is maintained until the peripheral white blood cell count is again around 15,000, the primitive cells are reduced greatly, and the red cells and hemoglobin increase. Bone marrow examination is a more exact check. Repeat courses can be given as indicated.

P^{32} therapy has been displaced somewhat by the trial of newer chemotherapeutic agents since P^{32} is only a palliative and not a cure. P^{32} when used properly is not too dangerous, causes very little or no reaction as does x-ray irradiation, and is not as toxic as many of the drugs. Many physicians now reserve P^{32} for the stage when other therapy does not effect relief for a sufficiently long period, though by this time one often finds nothing to be helpful, not even P^{32}. In the lymphomas, including lymphosarcoma and Hodgkin's disease, P^{32} therapy is usually disappointing. Carefully distributed on blotting paper, P^{32} is an excellent source for irradiation of superficial skin lesions and cutaneous hemangiomas. Almost all "strawberry marks" will regress spontaneously if left alone. This method, described by Low-Beer,[12] has been further refined in our unit by Roth and Castle (unpublished) and extensively used for skin cancers of adults.

Cobalt (Co^{60}) is an effective substitute for radium, but has been as little used in children as radium. Roentgen

rays are usually more applicable in the comparatively few conditions in which external irradiation is desired. Co^{60} is relatively inexpensive, is produced in sufficient quantities, and can be used in wires or as tiny "seeds" in nylon threads which can be seeded or sewn into lesions.

Colloidal Au^{198} (as gold chloride) or colloidal P^{32} (as chromic phosphate) are employed for treating malignancies in the peritoneal and thoracic spaces or for local injections into areas where distribution beyond such areas is nil or minimal, as in therapy by chromic phosphate for malignant lymph nodes. There are, of course, not as many cases in childhood as in adults, and surgery, roentgen-ray therapy, and chemotherapeutic drugs are first used. These radioisotopes are used in their colloidal form to localize and greatly minimize their transport to distant and undesired parts of the body. They are indicated particularly when the primary malignancy cannot be removed surgically or when it has recurred, or metastases have occurred. Colloidal chromic phosphate is displacing colloidal gold as the most desirable therapy. Colloidal gold is relatively more expensive, has a shorter half-life (2.69 days) than P^{32} (14.3 days), charges are greater because of the amount of shielding required during transportation, and because of its intense gamma radiation the hazard to attendants is greater during and following its administration to patients. The childhood dose of chromic phosphate can be 2 to 4 mc. for the thoracic cavity and 3 to 6 mc. for the peritoneal cavity. Its use is indicated in lymphomas, lymphosarcomas, endotheliomas, and x-ray-sensitive tumors. The fluid is first evacuated. Recurrence is not so quick after these radioisotopes are instilled, and patients feel more comfortable. There are no reactions, even though they are not usually cured. Several retreatments may be necessary at four- to six-week intervals, which is the time for the maximal radiation effect.

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Psychologic Aspects of Pediatrics

PARENT RESISTANCE TO NEED FOR REMEDIAL AND PREVENTIVE SERVICES

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MOTIVATION for remedial and preventive medical services is a highly complex process and as yet relatively few of its components have been identified. In connection with health supervision programs for well children, the McCormick Fund as a research foundation has been interested for a number of years in assessing major reasons why the physician's recommendations to parents are so frequently not carried out. A fruitful approach to some of the basic problems in preventive care was recently presented the foundation in an opportunity to review outcomes of a screening program for hearing and vision defects in a large metropolitan school system.* The results of this review merit thoughtful consideration of pediatricians in their private practice contacts as well as in their clinic activities.

Since much of the hearing disability in childhood is said to be preventable and most visual difficulties are correctible, what was done after parents were advised of the need for immediate medical attention offers a neat problem for inquiry into some of the factors involved in effective carrying out of referrals for remedial care. The data consisted of records from the hearing and vision conservation program in 128 Chicago public elementary schools covering the final twelve months of a two-year demonstration period during which key personnel were provided by private agencies to assist in launching the program.

Procedures for case-finding of children with impaired hearing included group and individual pure-tone audiometric tests over six frequencies administered by technicians followed by otological examination of all cases failing to meet the minimum test standard, with referral for treatment as indicated. Screening for visual difficulties was done with the Massachusetts Vision Test supplemented by observations reported by teachers of children exhibiting ocular symptoms.

In general the pattern of the program was laid out in three distinct but interrelated steps: (1) testing of pupils by technicians for hearing and

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visual difficulties; (2) interpretation to the parent of the child's need for professional care—in case of a hearing difficulty interpretation was by the examining otologist, in case of a suspected visual defect by a vision consultant; (3) follow-up on cases identified as having a hearing or visual problem, as carried out by home visitors or teacher-nurses.

During the period covered by the review, selection of schools where screening was to be done was determind by requests from the principals. Widely diverse environmental conditions were represented, ranging from very favorable residential sections of the city to blighted areas where dwellings are so deteriorated or deficient in basic sanitation as to constitute a health hazard. A total of 36,692 children in the kindergarten, first, fourth, sixth, and eighth grades were given hearing tests during the last year of the demonstration period. Of these, 2.8 per cent were referred for otological examination in the screening clinic, and 2.0 per cent of the pupils tested were found to have impaired hearing. Vision tests were administered to all pupils, with the exception of those wearing glasses, from kindergarten through eighth grade. Of 38,104 tested 15.5 per cent failed to meet minimum requirements of the test and their parents were advised to take them to an eye specialist.

In the 128 elementary schools screened for hearing and vision defects, 6,731 children were referred for professional attention because of loss of hearing or a suspected vision defect.

Children with impaired hearing, as diagnosed in the otological clinic, were as likely to be from the better residential neighborhoods where living conditions are favorable and family incomes are well above average as from underprivileged sections of the city. They were found at all age levels, among those just entering school as frequently as among those in their final year of grade school. In only a relatively small number of the cases had the families suspected any difficulty in hearing, although the loss was bilateral about as often as unilateral and in some instances was severe.[1]

Unlike hearing problems, the need for professional attention as detected by the vision test was indicated more frequently where living conditions were poorest. Visual difficulties, however, varied little with the age of the child. Test failures occurred about as frequently among beginners as among upper grade pupils.

A major objective of the program was adequate diagnosis with treatment as indicated for all cases suspected of having a hearing or visual problem and with educational opportunities provided to meet their special needs. What was done for the child after his parents were advised of his suspected difficulty was appraised in terms of information reported by the treating physicians to the school during a one-and-one-half-year to two-and-one-half-year period following the initial conference with the parent about the child's need for care. While it is recognized that school records probably do not reveal the full extent of follow-up, they provide the basis for the school's planning of special educational programs to meet individual needs of children with hearing and vision impairments. A limited check on the adequacy of these records was made by personal interviews with some of the parents of children for whom no reports on care

were available and with doctors for verification of statements as to services obtained. The available records can be said to present a generally unsatisfactory picture with reasonably good evidence that, despite comprehensive preliminary planning with medical organizations and parents themselves, a large proportion of the children discovered to need medical attention were never taken to the doctor.

Reports to the schools indicated that less than *two* out of every *five* pupils identified by screening procedures to require care were known to have been given an opportunity for correction or treatment—32.5 per cent of those referred from the otological examining clinic and 38.8 per cent of those with a suspected eye problem. On the basis of findings from personal interviews while these percentages would be raised, it is clear that many families did nothing about the recommendations for care and others delayed action for more than a year, often failing to mention the ear or eye difficulty when a visit to the doctor was made.[2]

Failure to follow through on recommendations for medical care is unfortunately not unusual, whether the problem concerns a physical condition or an involved emotional situation. It is not because parents are unconcerned about the welfare of their children that little or no effort is made to secure needed medical services. Unquestionably most parents want to do what is best for their children. Why, then, were parents seemingly unimpressed with the importance of proper care for specific impairments which they are aware may be possible handicaps to a child in his school progress and social adjustment? Some of the underlying reasons for their failure to take the child to a doctor were explored in the light of socioeconomic background, the type of defect suspected with its associated findings and history, the age of the child, and parent attitudes as revealed by their comments at the time of interview. Results of these explorations are briefly summarized here.

CORRELATES OF FOLLOW-UP ON MEDICAL RECOMMENDATIONS

Socioeconomic Status of Family.—Differential use of medical services has been investigated in a number of different settings with at times inconclusive or contradictory results reported. In general, however, economic factors have been shown to be influential in the keeping of appointments and continuing under care. Results from explorations in the present study likewise indicate a direct relation between socioeconomic status, as here classified, and action taken by the families to secure the advised medical services, but the degree of association is not close.

Physical characteristics of the neighborhoods and contacts of individual families with social agencies were used as indices of socioeconomic level. Neighborhood was defined as a census tract and the 1950 census data together with later special community surveys used to describe living conditions, population character, and family income level of each neighborhood. While place of residence may not afford an accurate index to family status, living conditions reflect the general quality of the environmental background of the children identified as having hearing or vision difficulties. Stability of the population, according to census reports for Chicago, is about

the same in the poorer sections of the city as in the better sections. In the exclusively white areas represented in the study, 87 per cent of the families in the poorest neighborhoods had not changed their place of residence during 1949 and 1950 as compared with 88 per cent in the best sections.

The trend of the findings suggests that the lower the family's socioeconomic status, the less likely was the child referred for care to be given an opportunity for corrections or treatment. In the most favored residential areas where the population was predominantly "Old American" white and family incomes were relatively high 57 per cent of the children referred were known to have received medical attention in contrast to only 28 per cent in underprivileged neighborhoods of similar population character. Among white families having a history of contacts with community social agencies for services other than financial assistance 38 per cent of the children referred were taken for the advised care; among those having a history of financial help 22 per cent of the children were taken for care.

Undoubtedly in some cases economic status was an influential factor in determining whether or not the recommended medical care was obtained but in the present study there was little indication that it was the major factor. For example, regardless of the socioeconomic level of the family the large majority of the children receiving care were taken to a private practitioner. Even in neighborhoods where living conditions were poorest (exclusively white population) and family incomes were low, at least three of every four families that took their children for the recommended medical attention went to a doctor in private practice. Ninety-two per cent of all care reported for white children was provided in doctors' offices. Also the evidence shows that high economic status of the family did not assure the child opportunity for needed medical services. More than 40 per cent of the families in the highest economic categories failed to get the child under care as advised—42 per cent when the problem was a visual defect and 55 per cent when it was loss of hearing.

When living conditions were similar, the Negro child was as likely to receive medical attention as the white child but he was usually taken to a clinic, regardless of the family's status. However, none of the Negro families included in the investigation were living in the better residential sections of the city.

Type of Problem and Severity.—On the whole, the nature of the child's problem seemingly had little bearing on whether or not the advised attention was obtained although certain comparative differences would seem to have interesting implications. The child with a vision problem appeared to have somewhat better chance of getting something done about his difficulty than the child with an ear disorder, although differences were marked only in cases from families of above-average status. A conductive type of hearing impairment, which usually involved the middle ear, was the most frequent type of hearing loss for which medical care was advised but children with such diagnoses were least often reported to have received any medical attention. Because conductive impairment is considered to be one of the most amenable to treatment of ear disorders, implications of

the failure to do anything about this problem after the parents had been informed by the examining otologist of his diagnosis and the importance of care for the condition would appear to have special significance for preventive medical programs.

Likewise, analyses offered little to indicate that severity of the impairment had any significant influence on action taken by the parents. Children with moderate or severe degree of loss in the speech-hearing range were no more likely to be taken for care than those with mild loss or whose hearing was normal in the better ear. Those having bilateral loss received no more attention that those having unilateral loss. Severity of hearing loss among the children referred for care varied from no loss in the speech frequencies (less than 20 decibels) in the better ear to an average loss of 75 decibels in the better ear.

History and Age Level.—With respect to history, there is some evidence of an association between previous knowledge of the impairment and extent to which remedial services were sought. Findings were fairly consistent at all status levels in suggesting more follow-up when parents had suspected a hearing or vision defect (according to their statements) or had known about it earlier and had had treatment. Of the children referred because of an ear disorder, 39 per cent of those for whom there was a history of ear trouble with treatment were taken to the doctor as recommended and 39 per cent of those who had had no treatment but who were suspected of having difficulty hearing, as compared with 28 per cent of those whose loss had not been recognized until the child was tested at school. Similarly, with children having eye problems, 52 per cent of those wearing glasses, who were advised to have a re-examination, were known to have been seen by a doctor as against 39 per cent of those referred because of failure to pass the vision test. In general, the findings reflect more readiness on the part of parents to carry out recommendations when their previous experience had convinced them of the importance of the advised services.

While these explorations certainly reveal no strongly motivating effect of previous knowledge of the child's problem, the trend of the comparative findings is suggestive of a contributing influence on what was done about the need for care.

Age at the time the hearing loss or visual defect was discovered was apparently unimportant in determining whether or not the child would receive medical attention. As many of the youngest as of the oldest were reported to have been taken to the doctor. Follow-up on children just entering school was neither more nor less frequent than on those in the upper grades. It would appear from these results that neither the parents nor the children were greatly impressed with the importance of doing something about the ear or eye disorders identified by screening procedures.

Relationship With Medical Care.—Findings of this study on relationships between care obtained, during a two-year period following recommendations for medical attention and various social and economic aspects of the child's background and of the nature and history of his impairment have, on the whole, thrown little light on conditions contributing to effective motiva-

tion for remedial care for the school-age child. The few positive relations observed may be but facets of more basic factors concerned with the readiness of families of different social and cultural groups to accept the concept of preventive medical services. Very interesting evidence has been reported from public health programs[3] and private clinics which indicates that the ways individuals use medical services vary with the person's cultural affiliations. Studies on the uses of psychiatric clinic services have revealed that the acceptance for therapy and the character of the patient's clinical experience are significantly related to his "social class."[4]

ATTITUDES TOWARD THE NEED FOR MEDICAL SERVICE

The reaction of parents to a diagnosis of impaired hearing or vision will vary with individuals but it will tend to influence what is done to alleviate or correct the condition. Some parents stated frankly, when advised of the suspected defect, that the child seemed to hear or see all right and they saw no reason to be concerned about him. While among families represented in the study such comments were rare, and perhaps were from some of the most uncooperative or the most disturbed because of personal feelings of guilt over the possibility of a handicap, they nevertheless may serve as clues to a greater reluctance in acceptance of the diagnosis than was generally assumed.

It is recognized that explanations given by parents for their failure to carry out recommendations for medical care may not reveal the true reasons for noncompliance. Defense against anxiety is probably one of the strongest motivating forces in human behavior and certainly being suddenly confronted with an unsuspected physical handicap of the child may give rise to mixed feelings which are not easily resolved. When interviewed, a number of parents voiced their alarm at the time they were first informed of the screening results but, since the child said he had no trouble in hearing the teacher or seeing the blackboard, they had put off the expense of a visit to the doctor until there were more pressing health problems. Others reported they took the child to his pediatrician for a health checkup but they had raised no question with him about hearing or vision, assuming that if there were an ear or eye disorder the doctor would discover it.

In instances where parents had been previously aware of the impairment, some expressed a relief from the urgency in securing treatment because the child was progressing well in school after the teachers understood his problem and had made an effort to alleviate the difficulties he faced in learning situations. Others seemed to accept the disabilities as something to be endured since they appeared to "run in the family." Interpretations by the examining otologist and vision consultant had given these parents no real understanding (or there was resistance to full acceptance) of the possibilities of correcting or offsetting the handicap with proper treatment and special guidance. It is not unlikely that the removal of the feeling of pressure to get the child under care and an attitude of hopelessness about the problem accounted for the failure of many of the severely impaired cases being given an opportunity for the recommended medical attention. In

this connection it is noteworthy that most of the younger children having a moderate to severe degree of hearing loss were taken to the doctor. It was usually the older children with this degree of impairment who received no medical care.

Interviewing was done by a social worker in the homes of children for whom no follow-up record was available. Cases for a small sample were so selected as to include children from widely diverse environmental conditions, of different ages, and having various types of ear or eye defects for which care had been advised. When the parent indicated to the interviewer that the child had been given medical attention, a release of the doctor's findings was requested and an interview with the treating physician arranged.

Individual records and interviews offer convincing evidence of the lack of intelligent understanding and appreciation on the part of many parents of the importance of early remedial and preventive services. More adequate interpretation of the practical values of preventive measures would seem to be required at all economic levels. Referrals from screening programs in schools place much of the responsibility for this interpretation on physicans and clinics, since the screening procedures are not diagnostic and consequently may refer some children needlessly. The resulting situation may prove to be frustrating to parents, more especially to those who are reluctant to accept the recommendation for medical attention.

Results of the present investigation indicated that about 18 per cent of the children who failed to meet the test requirements and who were later examined were found to have nothing wrong with their ears or eyes. To these overreferrals there was added another 10 per cent of referrals for eye care which, although an eye abnormality was verified in the judgment of the eye specialist it did not warrant treatment, either because the difficulty was insufficient to require correction or the condition could not be improved. From the viewpoint of many of the parents, the trips to the doctor for these children were a needless waste of their time and money.

Many of the comments from parents reflected the significant role the doctor's attitude and manner of handling the cases played in the parents' feeling about preventive services. This was e s p e c i a l l y evident in statements concerning the needless referrals and also of cases referred from the otological screening clinic for removal of cerumen with evaluation of hearing later. Numbers of these latter were seen by the child's pediatrician or the family doctor.

Attention is called to the fact that a relatively large proportion of the care obtained for the impaired hearing cases was provided by these general physicians. While in a number of cases the records show that the pediatrician advised the parent to take the child to an otologist, such recommendation apparently was not always made. It was clear from interviews with parents and physicians that numbers of the hearing impairment cases were never seen by an ear specialist, either in his private office or in a clinic, after the intial otological examination in the screening clinic.

Recent research in psychiatric clinic settings has emphasized variations in expectations of parents from different

social and cultural classes.[5, 6] Results of the hearing-vision follow-up suggest that much is expected of a doctor by parents from all sociocultural levels even to discovering the specific problem, whatever its nature, for which the child may need care. While the pediatrician must assume differing roles to try to fit mothers' varying needs, there may be a basic sameness in their expectations of him.

CASE ILLUSTRATIONS REFLECTING ATTITUDES INCOMPATIBLE WITH EARLY REMEDIAL CARE

CASE 1 (Follow-up by family physician and ear specialist).—Na., a 6-year-old girl in the first grade, had an audiogram reading showing an average loss in the speech frequencies of 30 decibels in the right ear and 45 decibels in the left. On examination in the otological screening clinic she was found to have a bilateral conductive type of impairment of the middle ear due to otitis media (serous), with associated findings of nasal allergy and lymphoid hyperplasia.

According to the mother there had been no history of ear trouble, but because of frequent lack of response and inattention, she had recently suspected some hearing difficulty.

Shortly after the child was examined at school she was taken to the family physician who was informed of the referral. He advised a tonsillectomy and referred her to an ear, nose, and throat specialist. Two months later Na. was taken to the specialist who considered removal of the tonsils inadvisable but began treatments which were continued through the year.

CASE 2 (Follow-up by ophthalmologist incidental to an accident).—Mi., a 9-year-old boy in the fifth grade, was referred for an eye examination because of failure on part of the vision test which is designed to detect muscle imbalance, and of observations of red swollen lids and a turning in of the right eye.

Nothing was done about the referral immediately but a few weeks later the boy got something in his eye and was taken to an ophthalmologist to have it removed. At that time the mother requested a thorough eye examination. Glasses were prescribed and fitted.

According to the mother, she has great difficulty getting him to wear the glasses. He claims they do not help him and she herself thinks they do little for him. She insists that he wear them when studying or watching television, believing that perhaps they may relieve some of the eyestrain.

The ophthalmologist's records show that there has been no contact with the case since glasses were fitted some two years earlier.

CASE 3 (Follow-up by otolaryngologist after long delay with no mention of referral from the screening clinic).—Gl., a 9-year-old girl in the fourth grade, was found by tests to have a mild degree of hearing loss in the speech frequencies in both ears. A tentative diagnosis was made of perceptive impairment with a referral for an evaluative study of hearing with treatment.

There was history of polio and ear infection with treatment at age 6. The mother was aware of the hearing problem and had endeavored to get the child's teacher to change her seat in the classroom. However, according to the mother's statement, the teacher did not think the child had any difficulty hearing, and not until the school otologist recommended a change in seating had anything been done about her request. The mother thought the child had profited greatly from the teacher's sympathetic understanding of the situation.

No immediate steps were taken regarding medical attention for Gl. as advised. but, when interviewed, the mother stated that after the clinic visit she had inquired among friends as to the name of an ear specialist to whom she should go. After a delay of nine months the child was seen by an

otolaryngologist but no mention was made of the examination in the screening clinic.

The specialist's record showed a conductive type of hearing loss of moderate degree with recurrent adenoid tissue sufficient to block the eustachian tubes. Following an adenoidectomy, the hearing was appreciably improved.

CASE 4 (Follow-up at ear clinic after long delay and appearance of bloody discharge).—Vi., a 6-year-old boy in the first grade with a moderate degree of hearing loss, on otological examination was found to have unilateral conductive type of loss due to otitis media (suppurative) with lymphoid hyperplasia. Recommendation was made for treatment with consideration of adenoidectomy.

There was history of discharging ears at age 4 and recent recurrence, but the parents had not suspected hearing loss. When interviewed, the mother stated that as her doctor had not been available she had delayed taking Vi. for care until he began to complain of earaches. He was then taken to a medical center where he was still receiving treatment.

Records at the medical center revealed that Vi. was brought to their pediatric clinic a few weeks after he was examined at school. At that time there was no mention of ear trouble or of referral from the school otologist. He was treated for hematuria and diarrhea following an upper respiratory infection. Three years later Vi. returned with a complaint of a bloody discharge from the left ear, but again no reference was made to the earlier finding on hearing loss.

The diagnosis was chronic suppurative otitis media on the left side with a perforation in Sharpnell's membrane. A secondary adenoidectomy was performed and the child was still under treatment in the ear clinic.

CASE 5 (Regular health checkup by pediatrician with no reference to special service recommended).—Ph., an only child in a family of comfortable circumstances, was 10 years of age and in the fifth grade when referred for eye care because of failure to pass the vision test.

When interviewed. the mother expressed her surprise and concern at the time she was informed of the suspected vision defect, since Ph. had had good pediatric care all of his life. She stated that she had taken him to his pediatrician shortly after she was advised of the need for medical attention.

The pediatrician's records showed yearly health checkups of Ph. with at least two visits since he failed the vision test. No question was raised about his vision. On the basis of findings from a general physical examination there had been no reason to suggest an eye examination by an ophthalmologist, which would have been done had the doctor known of the child's failure to pass a vision test at school.

Ph.'s mother had been informed in January of his need for an eye examination. He was not taken to a specialist and did not visit his regular doctor until the following August. It was two years later that the problem was brought to the attention of the pediatrician, although this mother had professed to be alarmed when she learned of the possibility of a vision defect.

COMMENTS

With the broad concept of health, now generally accepted, expectations of parents in their use of medical services are forcing increasingly heavy responsibilities upon pediatricians in serving their child patients. As physicians understand the motivating forces underlying these expectations they are better able to offer the assistance parents want and seek, but the task of acquiring this understanding is far from simple. The process of motivation is highly complex, involving the interplay of numerous factors, few of which have been disentangled from the

total pattern of behavior. From what is known, however, it is a safe assumption that the physician's personal reactions to the parent in the counseling situation exert a strong influence not only on what is done about his recommendations but, perhaps more significantly, on the general attitudes of the parent toward the value of early remedial services.

An excellent illustration of the less tangible influence of the physician on attitudes is that of the boy who had been under regular supervision of a competent pediatrician but when the mother learned of the possibility of a vision defect she waited seven months before she took him to his doctor. The apparent reason for the visit then was to have a health checkup before the boy left for summer camp. Similar situations were noted when the problem was impaired hearing. There had been repeated reminders by teacher-nurses of the need for professional attention for specific impairments but no mention of the school's findings was made when many of these children were finally taken to the doctor.

In the appraisal here reported of outcomes of a screening program for hearing and vision defects, the focus was on concomitants of noncompliance in follow-up of recommendations for medical attention. Explorations of certain environmental cues and personal attitudes as determinants of action taken have revealed few positive relationships. Action taken was defined as a visit to a physician or clinic, regardless of what was done about the suspected defect.

Some evidence of a relationship between socioeconomic status and compliance was indicated with a consistent trend of more follow-up where the environmental background was more favorable and income levels were higher. While such associations were to be expected, it was surprising to find a large proportion of so-called middle-class families in the upper income brackets failed to get their children under medical care as advised.

The primary value of case-finding of health problems lies in the possibility of prevention of disabilities and the fostering of healthy development. However adequate case-finding procedures may be, unless there is effective follow-up with remedial services and proper guidance, benefits accruing to individual children identified as in need of medical attention will be meager. It is recognized that primary responsibility for seeing that needed professional services are obtained is vested in the parents. In instances where parents, for whatever reason, fail to discharge their responsibility, community health services work against great difficulties or the child is forced to bear the effects of neglect. The impact on the child of knowing that his parents were told that he needed medical attention and then having nothing done about his difficulty will surely not be conducive to an appreciation of the importance of remedial and preventive services.

In studies of unmet health needs of a group of Chicago children from families receiving public assistance it was found that, if parents understand the significance of early remedial care to their children's well-being and if the process of securing the required services is not too difficult for them, the advised care was usually obtained. Adequate interpretation at the time of examination and continuously over the period of treatment appeared to be

important to the completion of treatment.[7] With many reminders and support from the family case-workers, 80 per cent of the recommendations were fully carried out.[8]

The results of the present investigation likewise suggest that much of the noncompliance on the part of parents from widely different "social classes" stems from a lack of intelligent understanding of what impaired hearing and vision mean to the child's well-being and what can be done to correct or alleviate the condition. The role of the child's physician in interpreting his difficulty to the parents would seem to be highly important. With respect to impaired hearing it should be emphasized that, while the parent may wish to have the advice of the pediatrician after being informed of the hearing loss, adequate medical diagnosis is essential and can be provided only by an ear specialist who is understanding of, trained in, and sympathetic to hearing problems.

SUMMARY

Interrelations of outcomes of a screening program for hearing and vision defects, where the major objective was adequate diagnosis with treatment as indicated and educational opportunities provided to meet special needs, with socioeconomic status and parent attitudes have been briefly discussed. In general, direct relations between social and economic aspects of family background and action taken to get the child under care were indicated, although the degree of relationship was not high. Also, previous awareness of the child's difficulty, with or without a history of treatment, appeared to be a contributing influence on what was done. Five case reports were presented as illustrations of parent attitudes toward early medical attention for hearing and vision defects.

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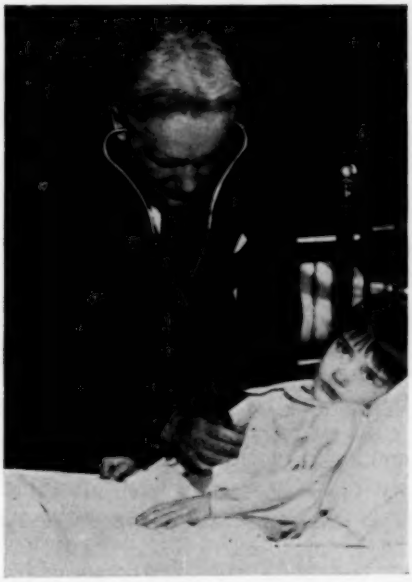
Pediatric Profiles

Frederic John Poynton

(1869–1943)



IN A certain hospital magazine a small section is devoted in every number to "Sayings of the Great," consisting of pithy remarks of the consulting staff on their teaching rounds. As a contrast, "Sayings of the Not So Great," amusing answers given by their students, are also recounted. Reading these as the years go by makes one realize that *obiter dicta* of the Masters are no longer so good, whereas the doctor in training is the same source of unconscious humor.

Poynton was in every way one of the old school. Essentially a humanist, he drove home the points he wanted to make by dry remarks which his students can still recount with a smile. If you ask any of the present senior staff of the Hospital for Sick Children, Great Ormond Street, which of their teachers made the greatest impression, Johnnie Poynton or Frederic John will almost unanimously be mentioned first. He combined the wit of Oliver Wendell Holmes with the best possible bedside teaching. Above all, he showed us how important it was to look at things from the point of view of the patient and to consider sympathetically the anxieties of the parent. In short, he taught us good doctoring.

Attending one of his rounds was always an experience. The inevitable inquiry, "Are you a doctor?" always preceded a question addressed to a fresh member of his class, probably not so much out of deference to his newly acquired qualification, but to avoid exposing any ignorance that might still remain. He took particular delight in these preliminaries when the object happened to be a notoriously chronic finalist who was having difficulty with his examinations. Then the laughter which greeted the query was enhanced by Poynton's serious demeanor, through which appeared a twinkle in his eye. He liked to tilt at

From the Hospital for Sick Children, Great Ormond Street, and University College Hospital, London, England.

his colleagues and was rather naughty about this, particularly when something very heavy was upset in the ward above and thundered onto the floor during his round. With an angelic smile and a hand cocked to his ear, he used to say, "Must be Dr. B. S. percussing a chest." The same impishness made him give suitable sobriquets to others, perhaps not so publicly expressed. Old "Marlin Spike" and our friend "the Elbow-Lifter" were no doubt appropriate and we all knew that "Shifting Dullness" referred to a physician whose visits were most boring and unduly prolonged. On his retirement to Weston, back in the county of his birth, he could not help being amused at the parochial outlook and starchiness of some of the doctors and local gentry in the famous city that lay near by, and always referred to them as "the Bath Buns."

His senior nurses were very faithful and never wanted to relinquish his wards, so much did they value his consideration. For teaching purposes, they kept a box of charts of unusual cases he had seen, and noteworthy drawings, collected in his practice and from some of his famous seniors such as Cheadle, to whom he paid great homage. These still exist, but the famous "brown book," his Researches on Rheumatism, the "red book," with clear illustrations of the nervous system, and the "green book," containing pictures of the fundus oculi in disease have passed into oblivion. They all served in their time to clarify our early impressions and emphasize his statements.

Treatment of the patient was always uppermost in his mind, which was heartening to young medical men who in some other quarters had seen physicians content with making brilliant diagnoses. Always prepared to try the effect of a new drug, he was sometimes led into the realms of patent medicines, where scientific application might be lacking, and yet therapy outside the standard pharmacopoeia often attracted him. Diet was stressed and his recommendations took into account the character and predilections of the patient. One old lady, for instance, was quickly recognized as an epicure, regardless of cost, and her delight can be imagined when she was advised only to eat the tenderer claws of a lobster and leave the tougher parts untouched.

It is appropriate here to state that Poynton, like nearly all his contemporaries, practiced pediatrics as a specialty and combined this with adult medicine. Thus he was able to follow the destinies of many of his child patients when they had grown up. This proved particularly valuable in his research on acute rheumatism.

What then were the antecedents of this remarkable man, who to the end retained his power of boyish enjoyment, his mischievous frankness of speech, his sincerity, his honesty, and love of children? He was born at Kelston Rectory, Bath, on June 26, 1869, one of a large family, which included a brother who was to become Master of University College, Oxford, and public orator, and a sister who for years was a Dame at Eton. Throughout his life he remained a countryman at heart, and a man of Somerset at that, and his handsome features, rather unruly head of hair, short and stocky figure seemed more at home in rustic surroundings than the stuffiness of London. He was educated at Marl-

borough and later became a Governor of that famous school. Here he soon showed his skill at cricket and ended by captaining the first eleven. Later he played regularly for his county side and held the curious record of leading the Somerset team after attaining to the sober dignity of a Fellow of the College of Physicians. Always convivial, he had the distinction of drinking Sammy Woods and Ranzitsinghi, two of the most famous cricketers of his time, under the table after a particularly grueling game.

In his cricketing days, he was always known as Joseph, and in the pavilion at Lord's during the big matches he would be affectionately greeted by many old friends. He played hockey for Middlesex and also enjoyed a game of tennis or squash, at which he was quite adept. Golf was never his strong suit, a cricketing forehand shot serving him badly in his drives. Field sports were not his only recreation; he was a music lover, a Fellow of the Philharmonic Society, and sang for many years with a rich tenor voice in the choir of St. James's Church. He was an enthusiastic collector and specialized in everything associated with ballooning from its earliest days. As I write this, I can gaze at a fine old colored print of Montgolfier's first ascent in a fire balloon in 1783 at Versailles in the presence of Louis XVI and Marie Antoinette, which was once in his collection. One of his prized possessions was a cricket ball which figured in a match against the Australians in which he played. This he presented in all its red glory, suitably mounted and inscribed, to a very select dining club of the College of Physicians to offset the many black balls which were almost invariably given whenever a new member was proposed.

His early medical prowess at St. Mary's Hospital, where vacancies were few at the time, eventually culminated in his election to the staff of University College Hospital and Great Ormond Street. It was at the latter that he was the happiest, and he devoted himself largely to its welfare and development.

He wrote widely on various aspects of pediatrics, including scurvy, acholuric jaundice, leukemia, cretinism, and the citration of milk feedings, but it was in rheumatism and heart disease that he made his greatest contribution. Throughout his life this was his main medical interest, and in 1913 he published in one volume with Alexander Paine the outcome of fifteen years of research. In this they propounded the theory that acute rheumatism was the result of a blood infection and direct invasion of the tissues by a diplococcus of the streptococcal group. Although this has never been confirmed, the close association of the streptococcus with acute rheumatism has stood the test of time, and as yet no one has propounded an entirely satisfactory explanation of the etiology. To Poynton and Paine, therefore, the credit remains of being the first to bring to light a streptococcal connection with the disease. Apart from the etiology, Poynton wrote and talked on many aspects of acute rheumatism, and his Bradshaw, Lettsomian, Harben, and Long Fox lectures were all centered on this subject. He was largely responsible for the first nationwide interest taken in the disease and the impetus to further research in its many problems. It was certainly his

continuous appeal that led to the establishment of special country convalescent hospital-schools for the better care of rheumatic children. In 1931, jointly with the writer of this appreciation, he published a book on *Recent Advances in the Study of Rheumatism*, and in 1930 his work in this field, and in pediatrics generally, was recognized by the award of the Dawson Williams Prize.

Poynton was always disappointed that his theories on the cause of rheumatism did not receive general acceptance. But his faith in the truth of his beliefs remained unshaken and he fought vigorously against the doubts expressed. His own words: "It is a glorious battle this rheumatism, the more you get into it, the more glorious it becomes and a dog fight" sums up the attitude he adopted. In response to certain skeptical criticisms he once rather bitterly remarked: "Don't expect anything from the English except a grunt." He regarded himself as the Nestor and Sir Galahad of the rheumatic child, as indeed he was, and felt proud of his "utterly independent mind, most dangerous to the common peace." These hard thoughts and prolonged domestic cares unfortunately clouded his declining years. Illness also smote this great sportsman of the past, and a cholecystectomy was followed before very long by attacks of angina, which eventually took his last wicket. Four years before this occurred he must have realized that all was not well, for he wrote: "Entering on my seventieth year sounds awful and after that it is only an extension of leave." He always scorned pomp and circumstance, but cherished the good things of life. Once at an official dinner when he was in danger of being placed at the High Table next to people he disliked, he was asked where he would like to sit. "Near the food" was his immediate answer.

Those who bore him much affection would like to forget his later gloomy moods, when he described one of his last lectures as "a collection of futilities, but as such, a very fitting end to my medical life," and remember him still debonair, driving rather recklessly his two small and rather decrepit cars, named in turn the "Yellow Peril" and "The Thunderbolt," often to assist someone in distress.

Unconsciously he wrote his own epitaph when he once said, "The best way to live was as a free lance and die as one, with all its tactlessness, but with all its straightness for good or evil."

Bernard Schlesinger.

Comments on Current Literature

EPIDEMIOLOGY OF HISTOPLASMOSIS

ADVANCES toward a better understanding of histoplasmosis have been made possible by the ingenious and persistent endeavor of a number of people, and by the intelligent use of the epidemiologic, laboratory, and clinical methods at hand.

Furcolow and associates,[1] long interested in histoplasmosis, have described the characteristics of thirteen epidemics of this fungus disease. However, their report in the July, 1955, issue of the *Annals of Internal Medicine*[2] is regarded by Furcolow and his group as "one in which complete studies were done not only of the human cases but also of the animals, and, in particular, the environment from which the infection was acquired." The outbreak which initiated this particular study occurred on a farm in Atcheson, Kansas, and involved a mother and father, their two sons, aged 3 and 6 years, and a younger brother of the children's father. Careful case histories of all five persons involved in this outbreak emphasized the remarkable variability in the clinical picture associated with the disease. The clinical manifestations varied according to age, but particularly according to the degree of exposure to the fungus-containing material, in this instance the dried droppings being removed from a chicken house unused for two years. While the young sons, 3 and 6 years of age, were definitely ill as a result of exposure to the fungus, and developed serologic and skin-test evidence of the infection, as well as x-ray changes characteristic of the disease, they did not appear very ill. The 27-year-old mother, when first seen, appeared to have been ill for some weeks, but had not remained in bed, possibly because of pressure of home responsibilities. The father, 30 years of age, developed what appeared to be influenza-like manifestations. The 16-year-old brother of the family head was the sickest one of all five family members, and it was he who had had the greatest opportunity for exposure to the dusty chicken droppings and debris removed from the chicken house. The tentative diagnosis in the case of this boy was "old-fashioned flu," but further studies indicated that actually he was suffering from histoplasmosis, and some of his symptoms were still present seventy days after onset of the illness. It was of considerable interest that, as revealed by follow-up serologic studies, positive precipitin and complement fixation tests persisted in this boy for a much longer period than in his relatives who were less severely ill as a result of the infection. A slow fall toward normal occurred in his serologic response, although both precipitin and complement fixation tests were still positive about twenty months following the onset of his illness.

In an effort to learn more about the epidemiologic features of this disease in general, and those of the particular outbreak, the authors collected samples of soil from various areas on the farm: inside the chicken house, just outside the chicken house, from fields where material removed had been spread, from the main barn, from wallpaper and plaster refuse resulting from reconditioning the house, etc. Positive cultures for *Histoplasma capsulatum* were obtained from samples of soil collected inside the chicken house, and just outside the chicken house in the area where material had been dumped

in the process of cleaning. A significant link in the epidemiologic chain of events was provided by the isolation of *H. capsulatum* from samples of air obtained at a level two feet above the dirt floor inside the chicken house, and at a level six inches above the ground on the north side of the chicken house away from the dumping area. These air samplings were obtained by means of a Venturi sampler. Isolation of the infectious agent from air was accomplished by the use of laboratory mice.[3] This isolation represents the first recovery of *H. capsulatum* from the air at the site of a known outbreak of the disease.

Studies of animals in the area were also of interest: two of three cattle showed reactions to skin-test material for histoplasmosis; one of twenty-seven chickens tested was found to be positive to skin-test material; however, none of these chickens showed the actual presence of fungus in the tissues. Of eleven dogs, known to romp in the area of the chicken house, four showed positive skin tests for histoplasmosis, and five had positive cultures for *H.* capsulatum. One older cat showed a positive culture. Studies were carried out on various other animals within a two-mile radius of the farm on which the family epidemic occurred. Of 161 such animals, about 6 per cent proved to be histoplasmin-positive: six cattle, one mule, and two chickens, or nine reactors among 161 animals. These carefully executed investigations bear out the general impression that the fungus, *H. capsulatum,* tends to be present, and to persist, in the dried droppings of chickens, and that disturbance of this dried material permits the fungus to be suspended in air. When susceptibles are exposed to air containing this infectious agent, infection can occur, not only in human subjects, but in dogs and cats, as evidenced by primary isolations of the agent from these two species, and in chickens and farm animals (cows, one mule), as evidenced by positive skin reaction to histoplasmin. On the basis of these results obtained by Furcolow and his co-workers, it would appear that chickens are not important reservoirs, per se, but rather that the environment of chicken houses provides conditions favorable for this organism.

Another well-studied outbreak of histoplasmosis is reported in the *Journal of Laboratory and Clinical Medicine* for October, 1955, by Adriano, Schwarz, and Silverman[4] of Cincinnati, Ohio. In this instance, two children, aged 2 and 4 years, were exposed by residing for a period of about six months (March to September) and by spending week ends on a farm eight miles from their home in Reading, Ohio. Subsequent epidemiologic studies indicated that *H. capsulatum* was present in the environment of an abandoned reconditioned barn in which the family lived, and in an old chicken house which had been converted into storage space and into indoor play space for the children. Both children developed disseminated histoplasmosis, and both died. At the time of autopsy the diagnosis of disseminated histoplasmosis was established by cultures of blood, bone marrow, and lymph nodes. Close questioning of collateral relatives revealed that several adult persons making visits to the farm during the reconditioning process had suffered from "atypical pneumonia," the illness in one grandmother lasting for eight weeks or longer.

Two dogs living on the farm showed positive skin reaction to histoplasmin introduced intradermally, and were sacrificed for autopsy study. Both dogs showed evidence of disseminated histoplasmosis, and in the case of one, *H. capsulatum* was recovered by culture of liver and spleen tissue. No strains of *H. capsulatum* could be recovered from soil samples collected repeatedly in this area. However, it was of significance that a dog showing negative histoplasmin skin test, which was brought to the farm intentionally in February, 1953 (following the children's onset of illness in December, 1952), became skin-test positive to histoplasmin by June, 1953, a period of about five months. This dog was sac-

rificed for study, and showed on autopsy widely disseminated histoplasmosis, organisms being cultured freely from various tissues of the animal. It seems apparent that the farm environment of these two children with fatal disseminated histoplasmosis was the site of exposure, especially since a healthy dog, histoplasmin-negative, became positive and showed disseminated histoplasmosis within about five months after being introduced into this particular environment.

Such studies as these are significant for all who may be interested in the natural history of infection, but should serve also as a special warning particularly to city dwellers, who, when they acquire a country place, are prone to pursue vigorously the task of cleaning various buildings which may have been neglected or unused for some months. It seems reasonable that all unnecessary exposure to dust-laden air in such rural settings should be avoided, especially when it becomes necessary to remove debris and desiccated droppings from abandoned chicken houses.

RUSSELL J. BLATTNER

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News and Notes

Dr. Julius H. Hess of Chicago died November 2, 1955, at Los Angeles. He was 79 years of age. He was graduated from the Northwestern University Medical School in 1899 and started practice in Chicago in 1902. In 1908 he limited his practice to pediatrics. From 1913 until his retirement in 1944 he was professor of pediatrics and head of the department at the University of Illinois Medical School. Much of his work was at the Michael Reese Hospital where he developed the Hess incubator, and founded the premature-birth station. He became an authority on the premature infant and was the author of two books on the subject: *Premature and Congenitally Diseased Infants;* and the better-known *Physical and Mental Development of the Prematurely Born.* Three years ago he received the Borden Award of the Academy of Pediatrics for his work with premature infants. He was active in local medical and pediatric societies and for a number of years served on the Advisory Board of the Children's Bureau. He was elected to membership in the American Pediatric Society in 1921, and was a Founder member of the American Academy of Pediatrics. In World War I he served as Major in the Medical Corps.

Dr. Albert D. Kaiser of Rochester, New York, died November 1, 1955, of coronary disease. He was 67 years of age. He received his medical degree from Harvard in 1913. For many years he had a large practice in Rochester and taught at the University of Rochester Medical School where he was associate professor of pediatrics. In 1944 he retired from practice to become City Health Officer and was appointed professor of Child Hygiene at the Medical School. All of his life he was an active leader in community health and welfare organizations. He was a member of the American Pediatric Society and the American Academy of Pediatrics.

The following were certified by the American Board of Pediatrics at the examination at Chicago, Ill., Oct. 7, 8, and 9, 1955.

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Dr. Thomas Ault Anderson, 2605 B Hardaway Blvd., Isle of Palms, S. C.

Dr. Ona Mae Ricketts Austin, Gilbert and Roberts Clinic, 101 S. Iowa, Irving, Texas.

Dr. Harold C. Ball, 967 "B," Hayward, Calif.

Dr. Edith Muriel Bennett, Box 11, Kentfield, Calif.

Dr. Stanley Berlow, 4428 N. Stowell Ave., Milwaukee, Wis.

Dr. William David Bevis, Department of Pediatrics, University Hospital, Minneapolis 14, Minn.

Dr. Daniel Kenneth Billmeyer, 605 High St., Oregon City, Ore.

Dr. James A. Caddy, 54 Heather Lane, Levittown, N. Y.

Dr. Flossie Cohen, Children's Hospital of Michigan, 5224 St. Antoine St., Detroit 2, Mich.

Dr. Eleanor Colle, Department of Pediatrics, University Hospitals, Minneapolis, Minn.

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Dr. Vernell W. Curry, 413 W. 17th St., Pueblo, Colo.

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This year's refresher course for qualified pediatricians at **Tulane**, entitled "Pediatric Neurology," February 27 through March 3, 1956, will have as its guest speaker Dr. Douglas Buchanan of the University of Chicago. A comprehensive program will deal with basic considerations and clinical management of convulsive disorders, degenerative diseases of the nervous system, infections of the brain and meninges, and other such broad subjects. Selected members of the entire medical school faculty will participate, and stress will be placed mainly on clinical aspects of neurological disorders of early life. Those interested should apply to: Director, Division of Graduate Medicine, 1430 Tulane Ave., New Orleans 12, La. Registration, as usual, is limited to forty qualified specialists.

The twenty-fourth annual series of the Benjamin Knox Rachford Lectureships will take place in Cincinnati, Ohio, on Tuesday and Wednesday evenings, Feb. 14 and 15, 1956. Dr. Robert J. Huebner of the National Microbiological Institute in Bethesda, Md., will deliver these lectures in the auditorium of the Children's Hospital Clinic and Research Building. The titles of his lectures are (1) "The Opportunities and Problems of Modern Virus Research" and (2) "The APC and Coxsackie Virus Infections of Childhood."

Books

The Management of Acute Poliomyelitis. C. P. Stott and M. Fischer-Williams, Baltimore, The Williams and Wilkins Co. Price $3.00.

This short discussion of the practical management of poliomyelitis is written especially for British readers and is directed toward nursing care and over-all management of the early stages of this disease. Readers in this country will encounter unfamiliar drug names, unfamiliar and unavailable types of respirator equipment, and many items of lesser importance which are not in current use here.

This book has obviously been written on the basis of an experience which does not completely parallel that reported by many authorities in this country and there is much divergence from methods of patient care advocated by most American contributors to this subject. Details of management of the bulbar case, less emphasis on tracheotomy in meeting the difficulties of impaired function of palate, pharynx, and larynx, and different methods of management of disturbance of bladder and bowel function are quite at variance with those commonly employed in the United States.

The discussion of routines of nursing care and description of methods designed to assist with the restoration of muscle function without the employment of expert physical therapists are well worth reading.

This book will not serve as a primer for either the nursing care or medical management of acute poliomyelitis under the conditions which obtain in America, but the problems are the same everywhere, and careful reading will reveal many suggestions of real value and interest.

Feeding Your Baby and Child. Benjamin Spock, M.D., and Miriam E. Lowenberg, Ph.D., Boston, 1955, Little, Brown, and Co., 226 pages. Price $3.75.

An excellent book for mothers on the feeding of infants and young children which will undoubtedly become a "best seller" in its field. "Spock" is almost a household word, and Dr. Lowenberg is a nutritionist with an extensive experience in the feeding of young children. It is obvious that the first 75 pages are largely Dr. Spock's work. He presents the feeding of the infant, the preparation of the formula, and the addition of solid foods in a rather chatty sort of a way that makes it appear simple if one uses commonsense. He is not rigid, and his advice and suggestions are sound. Nearly 100 pages are obviously the work of Dr. Lowenberg as they present practical recipes for making food attractive to children, sample diet lists and

menus. The text, however, does not represent two separate contributions. Drs. Spock and Lowenberg worked together for four years at the Rochester Minnesota Child Health Institute under the late C. A. Aldrich, to whom the book is dedicated. Dr. Aldrich, despite the fact that his philosophy on physician-parent teaching was that the teaching of attitudes was more important than teaching details, would have liked the book.

B. S. V.

The Prevention of Disease in Everyday Practice. Isadore Givner, M.D., and Maurice Bruger, M.D., St. Louis, 1955, The C. V. Mosby Co., 964 pages. Price $20.00.

This text, edited by an ophthalmologist and an internist, consists of thirty-three chapters by different authors on the preventive aspects of various diseases: thus Chapter 1, A Practical Outline of Cancer Prevention, by Wynder; Chapter 2, Prevention of Poisoning —Accidental and Intentional, by Press; Chapter 3, Preventive Pediatrics, by Ginandes, and so on. The book is intended for the practitioner, and some of the discussions are excellent. However, the authors, for some reason or other, have seen fit to include subjects that are unimportant from the prevention standpoint to the practitioner, as "Preventive Aspects of Neurological Surgery" and "Preventive Aspects of Cardiac Surgery," which are technical subjects of interest and importance to the neurological and cardiovascular surgeons, but do not concern or interest the practitioner. In such instances the discussion is puerile so far as neurological and cardiovascular surgeons are concerned, and would not be the slightest value to the trained specialist in these fields. While the idea of the text is good, the editors have produced a large unwieldly text which is so padded with material that should have been left out, that they have succeeded in producing a book of little interest and value to the practitioner.

The Pediatric Years. Louis Spekter, M.D., Springfield, Ill., 1955, Charles C Thomas, 734 pages. Price $12.50.

The Director of the Bureau of Maternal and Child Hygiene of the Connecticut State Department of Health, a well-trained pediatrician who has also been certified by the American Board of Public Health, has written an unusual text on pediatrics. It is not intended for physicians or even nurses, but rather for the group of social workers, teachers, physical therapists, educators, and others who work with children, but who have not had medical experience in their training. It attempts in simple language to discuss the diseases of childhood with stress on the preventive side. We know of no similar book, and the author is in a much better position to judge of its need. It is a difficult task to present technical medical subjects in a simple way and, as a whole, the author has done a good job. Our chief criticism is that the discussion of many subjects is too extensive, and that the author has included many rare and uncommon as well as common diseases. Details as to specific treatment have carefully been avoided. The book is intended as a work of reference, and an excellent glossary has been included. It will be interesting to follow the reception of the text.

Child Behavior. Frances L. Ilg, M.D., and Louise B. Ames, Ph.D., New York, 1955, Harper & Brothers, 364 pages. Price $3.95.

Both authors are well known for their association and work with Arnold Gesell at the Yale Clinic for Child Development, and since 1948 the Gesell Institute for Child Development. This "popular" book on behavior and behavior problems is based on a widely read syndicated newspaper column started by the authors in 1951. The text, however, is not a reprint of the newspaper discussions. While there is nothing particularly new, or at variance with current thought, the authors, through the experience in writing for the laity, have produced a sound readable book which measures up with the better texts for parents.

Cardiovascular Surgery. Edited by Conrad Lam, M.D., Philadelphia, 1955, W. B. Saunders Co., 553 pages.

The papers presented, together with discussion, at an international symposium held at the Henry Ford Hospital in Detroit in March, 1955. The papers reflect the tremendous development that has taken place in cardiovascular surgery in recent years, and will be of great value and interest to those working in the field of cardiology. Most of the leading figures in the field from Europe, Canada, and the United States were present and took part.

Editor's Column

CLINICAL PATHOLOGICAL CONFERENCES

THE JOURNAL is happy to announce a new monthly department which starts with this issue—Clinical Pathological Conferences from the Children's Medical Center in Boston. The Conference reports have been prepared and edited by Dr. Sidney Farber, pathologist to the Center, and his associate, Dr. John M. Craig. The CPC is regarded as one of the most important and interesting methods of medical teaching. The wealth of material at the Children's Center in Boston, the breadth of interests of its staff, together with the outstanding work and leadership of Dr. Farber in the pathology of childhood make these Clinical Pathological Conferences of unusual interest and value. The diagnosis is not given at the start. The history of the case, followed by the discussion, gives each reader the opportunity of testing his own diagnostic acumen and knowledge. There is no question in the Editor's mind but that the CPC will be a department that will be looked forward to each month by our readers. Not only the JOURNAL, but pediatricians throughout the world, owe a debt of thanks to the Children's Medical Center and to Dr. Farber for making this material available to all.

PEDIATRIC PROFILES

JUDGING from personal remarks and letters, one from as far away as Australia, the "Pediatric Profiles" which were started in 1954 have been enjoyed by many of our readers. Several have made the suggestion that their original scope be extended to include European pediatricians who have played an important part in the development of pediatrics. The idea was discussed with some of our European colleagues and their reaction was most favorable. Accordingly, a list has been prepared by the Editorial Board and already authors for over ten have accepted our invitation to contribute a specific profile. While there are still a number of American pediatricians whose Profile has not been published, the d e c i s i o n was reached to publish the Profiles in the order of their receipt regardless of nationality. We are privileged to present in this issue a Profile of a British pediatrician, Dr. Frederic John Poynton, of rheumatic fever fame, by Dr. Bernard Schlesinger, Physician to the Great Ormond Street Hospital in London. It is our feeling that these intimate pictures are not only good reading, but that the collection as a whole will make an important historical contribution.

MEDICAL VERSUS SURGICAL TREATMENT FOR PYLORIC STENOSIS

THE swing of the therapeutic pendulum for pyloric stenosis forms an interesting chapter in pediatric therapy. Going back some forty to fifty years, the treatment was medical. It consisted of the use of atropine as an antispasmodic, to which later "thickened feedings" were added. The mortality was high, 30 to 50 per cent. Part of this mortality was undoubtedly due to our lack of knowledge at that time of the metabolic changes resulting from the vomiting and starvation, and available means for their correction. The few early surgical operations we recall, when an attempt was made to relieve the condition by a gastroenterostomy, were disastrous. Then the Fredet-Ramstedt operation was introduced, and this simple muscle-splitting operation changed the entire picture. While the mortality varies in different clinics, in clinics with a large experience in the preoperative preparation and the postoperative feeding the mortality rate is less than 1 per cent. As a result, surgical treatment today is used in practically every hospital and clinic in the United States. When the practitioner makes the fairly easy diagnosis his first thought is to get the infant into a hospital and have him operated upon as soon as possible. Only those who practiced in the pre-Ramstedt days can fully appreciate the dramatic change that took place. Not only is there a rapid cessation of the vomiting, but we no longer see the severely malnourished infants who survived under medical treatment. The medical student of today in the United States is taught only surgical treatment, and the pre- and postoperative care which falls on the pediatrician.

In some European clinics, particularly the Scandinavian and British, there has been a trend in recent years to return to medical treatment. Wallgren[1] in 1940 and Dobbs[2] and Mackay[3] in 1941 reported on the use of Eumydrin (methyl atropine nitrate) which they considered superior to the atropine derivatives previously used. Subsequently a number of reports on its use have been published. Schäfer of Hamburg in the recent (1954) *Franconi and Wallgren* text states that conservative (medical) treatment—good nursing, frequent small feedings, hydration, barbiturates, and Eumydrin—should be tried first, and surgery be resorted to in case the infant does not show signs of improvement in a few days. Both Ward in *Holt and McIntosh* (1953) and Nelson in *Nelson* (1954) discuss the medical treatment with methyl atropine nitrate, but favor surgical treatment. American clinics have not taken to the medical treatment with Eumydrin. Their feeling or attitude has been that as so many of the medically treated cases in the reported series eventually came to surgery (e.g., Malmberg, seventeen in seventy-seven; Dobbs, twelve in forty-three) medical treatment was simply a waste of time in view of the low mortality with surgical treatment.

In 1944 Nyman[4] of Sweden developed a new drug, methyl scopolamine nitrate, known as Skopyl, which was found to have a greater effect on the smooth muscle of the intestine and was without the troublesome dryness and mydriasis of the atropine group. In 1949 Malmberg[5] reported on its successful use in fifty-nine cases of pyloric stenosis. One infant died of gastroenteritis but none required operation.

In the last number of the *Archives of Disease in Childhood* (August, 1955), Corner, of Bristol, reports an interesting and, in a way, somewhat amazing series of 117 unselected cases of pyloric stenosis treated medically with Skopyl. There was only one death, the tenth in the series when the dosage was only one-half that used later, and only one case, the twenty-fourth, when the medical treatment was unsatisfactory and a Ramstedt operation had to be performed. In seventy-five of the 117 cases vomiting stopped immediately after the drug was started, and in nineteen more it ceased within forty-eight hours. In only twelve cases vomiting persisted after five days. A strict feeding regimen similar to that used postoperatively must be maintained. No toxic side effects from the drug were observed.

Whether or not the pendulum will make a full swing, and medical treatment replace surgical treatment as a matter of choice is, of course, a matter of conjecture, and will depend on further experience with Skopyl. Certainly the brilliant results of surgical treatment can no longer be compared with medical treatment as we knew it in the past.

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